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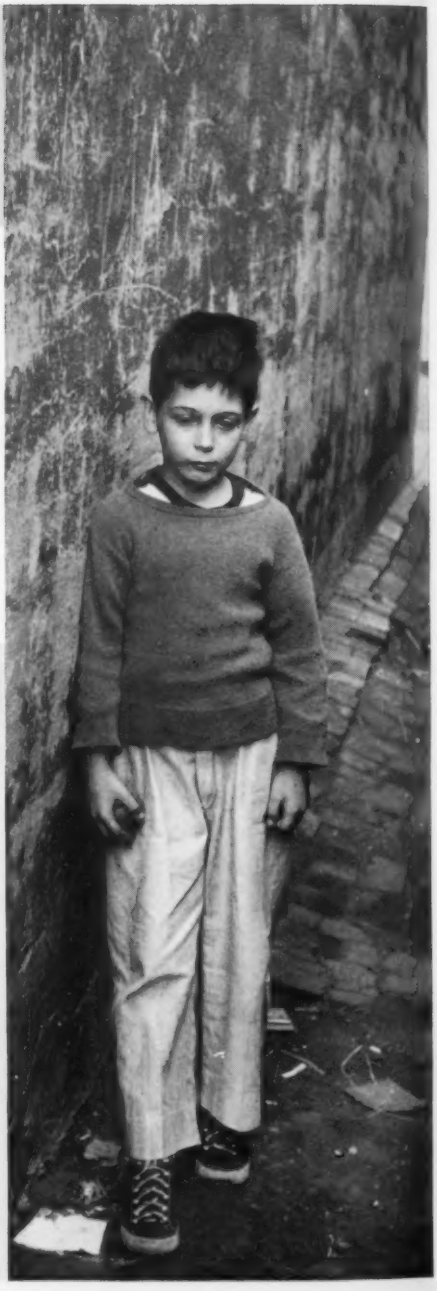

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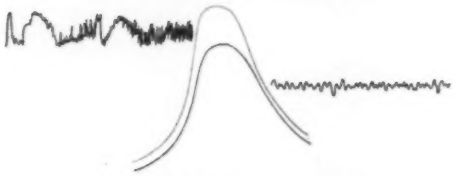

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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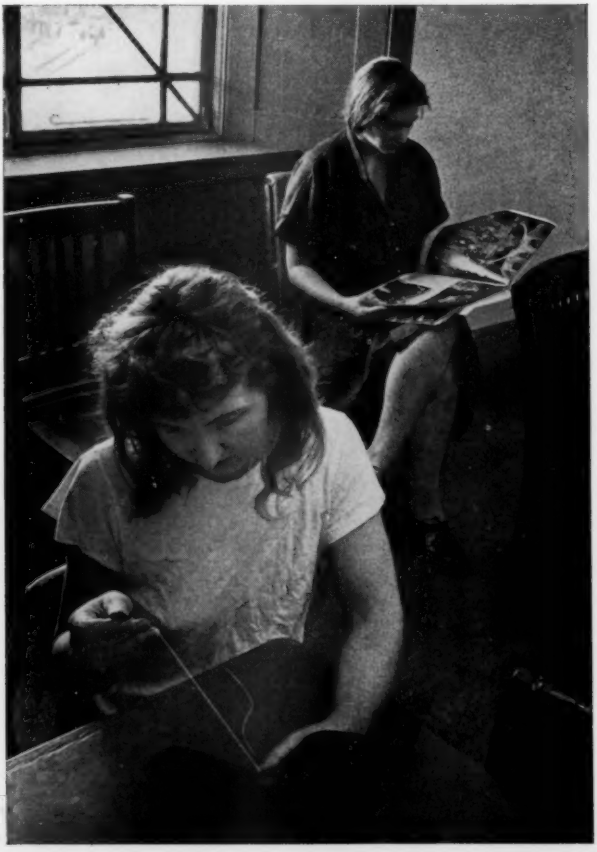

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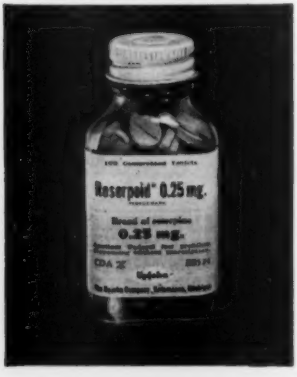

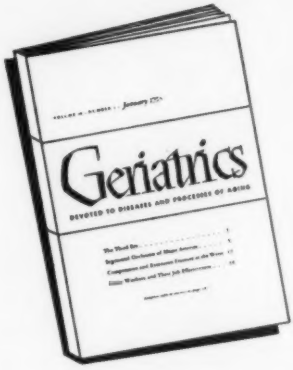

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1. Overholser, W.: in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.
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Volume 6 Neurology *Number 11*

Evaluation of Surgical Therapy of Disorders of the Basal Ganglia

H. Houston Merritt, M.D.

PRIOR TO 1926 the accepted forms of medical therapy for the abnormal movements and the disorders of muscle tone which accompany disease of the basal ganglia included atropine, hyoscine, stramonium, or scopolamine, all of which are extracts from the leaves of the solanaceous plants. In the past 20 years a number of synthetic compounds have been introduced and at the present time new ones are being added at a rate so fast that it is difficult for the practicing physician to keep pace with their progress. Each new compound is heralded as superior to the former ones in that it is more effective in relieving the symptoms or because it produces less untoward side reactions. It is quite true that the use of a new compound is often attended by a subjective improvement in the state of the patient, but it is difficult to measure this improvement objectively and often the subjective improvement is not maintained. It is not strange, therefore that some physicians raise the question whether the beneficial results of these medical agents are not due in part at least to the enthusiasm of the physician administering the compound and to the confidence of the patient in the physician and his treatment.

Discounting this so-called psychologic effect of the drugs, there is no doubt that medical therapy is of definite benefit to patients with muscular rigidity and alternating tremor associated with paralysis agitans, particularly in the early stages. It must be admitted, however, that the degree of improvement is often quite meagre in far-advanced cases of parkinsonism and that medical therapy is of little value in the treatment of patients with choreiform, athetoid, ballistic, or dystonic movements.

From the department of neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute of the Presbyterian Hospital, New York City.

Read at the eighth annual meeting of the American Academy of Neurology, St. Louis, April 26, 1956.

Inadequate results of medical therapy inevitably lead to attempts to modify the symptoms of diseases of basal ganglia disease by surgical methods. The disabling and progressive nature of the symptoms can be considered sufficient justification for the risks inherent in sectioning tracts or destroying limited portions of the nervous system.

The first successful operation for the relief of abnormal movements was reported by Horsley[1] in 1909. He resected the motor cortex of the contralateral side in a patient with athetosis. Following Horsley, many surgeons[2–24] have attempted, with various types of surgical procedures, to affect the abnormal movement and muscular status of patients with disease of the basal ganglia. The inadequate state of our knowledge with regard to the pathologic changes and the pathophysiology of the symptoms in parkinsonism and other diseases of the basal ganglia has made a rational approach to the problem difficult and explains the variety of avenues of attack which in former years included: 1) sympathetic ramisectomy, 2) section of posterior roots, 3) section of the posterior funiculus of the spinal cord, 4) section of the ventrolateral extrapyramidal tracts in the spinal cord, 5) section of the lateral pyramidal tracts in the spinal cord, 6) removal of portions of the cerebellum, 7) section of portions of the cerebral peduncles, 8) section of the internal capsule, 9) removal of the head of the caudate nucleus, 10) removal of portions of the motor cortex (Broadmann's area 4), 11) removal of portions of the premotor cortex (Broadmann's area 6), 12) incision of the cortex between areas 4 and 4-S (the supposed suppressor strip), and 13) prefrontal lobotomy.

Favorable results have been reported by the surgeons who devised many of the above operative procedures, but it can be said that the results obtained by one surgeon have not always been duplicated by others supposedly using the same technic. It may also be added that no one of these procedures has received general acceptance, nor have they given any information of value in the elucidation of the pathophysiology of the symptoms of basal ganglia disease. In fact, it was the generally accepted conclusion that beneficial results, when obtained, were related to injury to the corticospinal connections substituting a hemiplegia or mild hemiparesis for the more disabling abnormal movements or rigidity, and that with the disappearance of the hemiparesis there was almost inevitable return of the former symptoms.

In recent years the attention of the surgeons has been directed toward destruction of certain portions of the basal ganglia (particularly the globus pallidus) and their outflow. The introduction of the use of stereotaxic instruments in the human has aided progress, but they have not been used extensively as yet. The largest series of cases reported to date were operated upon without the use of these instruments.

It is too soon to draw any final conclusions with regard to these operations which destroy the globus pallidus or its efferent connections, but it is considered desirable to review in detail some of the reports in the recent literature.

Meyers in 1942[25] was the first to report beneficial effects as a result of section of the ansa lenticularis in patients with parkinsonism. In 1951[26] he summarized his results with various types of operative procedures in 54 patients. Section of the pallidofugal fibers only

was performed in 15 patients with the following results: much improved three, improved seven, unimproved two, and operative mortality three.

Narabayashi and Okuma in 1952[27] using a stereotaxic instrument, reported the effects of blocking of the globus pallidus with procaine in oil and wax. In 1956 Narabayashi, Okuma, and Shikiba[28] published the results in 26 patients with parkinsonism who had been observed for more than 18 months following operation. Tremor and rigidity were greatly improved in all cases, but the tremor tended to return to its former level within a few weeks. Reduction in severity of the rigidity was maintained for periods of observation varying from 18 to 32 months. There was a slight return of rigidity several weeks after operation, but it was much less severe than that present prior to operation. There was one operative death. "Supranuclear palsy" occurred in some cases (number not given), but this was said to be transient. The operation was performed on both sides in several cases of bilateral parkinsonism.

Fenelon and Thiebaut in 1950[29] coagulated the pallidum and nearby pallidofugal pathways, and in 1955[30] reported the results in 60 patients with parkinsonism and one patient with choreoathetosis. Good results were obtained in 70 per cent of the patients who were followed for periods varying from six months to four years. There were two deaths.

Cooper in 1953[31] reported that alleviation of the resting tremor and rigidity of parkinsonism could be obtained by occlusion of the anterior choroidal artery. It was speculated that this improvement might be due to ischemic necrosis of the medial portion of the globus pallidus and certain other subcortical nuclei. In a recent report Cooper, Poloukhine, and Morello[32] stated that good results were obtained in 60 per cent of patients subjected to this operation. There were five deaths, three postoperative hemiplegias, one case with aphasia, three cases with transient oculomotor nerve palsy, and one with hemianopia in this group. Cooper stated that the good results obtained in his patients had been maintained for periods of observation which extended over two years in some cases. Cooper's results with this operation have not been confirmed by all observers.[33] The difference in reported results may possibly be explained by variations in the origin and distribution of the anterior choroidal artery.[34] The inapplicability of this technic to elderly patients led Cooper to devise another method of destroying the globus pallidus, which will be discussed more fully later.

Guiot and Brion[35] in 1953 reported the results of destruction of the globus pallidus by a subfrontal approach in 40 patients with parkinsonism and seven patients with abnormal movements of other types. Three patients with parkinsonism died, two were worse, nine improved, and in 17 the operation was successful. Improvement resulted in two adult patients with chorea, but there was no improvement in the five patients with choreoathetosis dating from infancy. Complications of this operation included hyperthermia for four to ten days in 16 patients, euphoria in 19, depression in three, and transient Wernicke's aphasia in nine of 20 patients with left-sided operations. Hyperthermia and cerebral hemorrhage were the causes of death in three fatal cases. In 1955 these authors[36] reported that return of symptoms in

some of their cases had reduced the favorable results in the first 40 cases of parkinsonism from 42 to 37 per cent. The percentage of favorable results in the second series of 40 cases was given as greater than 60 per cent. They emphasized the fact that the operation was most effective in patients with unilateral parkinsonism and that bilateral operation was dangerous and contraindicated because of mental complications.

Spiegel and Wycis in 1954[37] reported the results of electrocoagulation of the ansa lenticularis in six patients with parkinsonism. Tremor disappeared in two patients. In one it reappeared after 11 months, to disappear again when the lesion was enlarged. In one patient the tremor was affected for only four weeks. In another only the tremor of the hand was affected. In the sixth patient the tremor was diminished in amplitude. The authors suggested that the parkinsonian tremor is due to release of the reticular substance of the midbrain and rhombencephalon from inhibiting impulses originating chiefly, but not exclusively, in the substantia nigra. At least a part of the pallidofugal impulses have a facilitating effect on the tremorgenetic area of the reticular substance.

Klein[38] reported improvement in two cases of choreoathetosis following electrocoagulation of the ansa lenticularis with stereotoxic apparatus.

Cooper[39] and Cooper and Poloukhine[40] in 1955 reported the results of unilateral destruction of the globus pallidus with alcohol (chemopallidectomy) by means of a catheter introduced under roentgenographic control in 70 cases, including arteriosclerotic and senile forms of parkinsonism. Lasting alleviation of tremor and rigidity on the side opposite to the lesion was observed in 70 per cent of the cases. Complications of the operation included hemiplegia in one case, slight residual hemiparesis in one case, ataxia and oculomotor nerve palsy in one case, and transient motor weakness lasting from one to three weeks in several patients. There were two operative deaths as a result of intracerebral hemorrhage. In their latest paper Cooper and his associates[32] report good results in 70 per cent of 125 patients on whom the operation of chemopallidectomy was performed.

Schwab and England[41] have made an independent study of 33 patients subjected to operation by Cooper. They state that a lesion placed in the globus pallidus can produce 60 to 80 per cent improvement in tremor and rigidity on the contralateral side which persists as long as they have followed the patients and, therefore, they would expect, indefinitely. This improvement is accompanied by better strength, power, and usefulness of limbs. There does not seem to be any significant change in the facies, excessive salivation, blink rate, speech, or ability to perform combined motor acts. In some patients there seems to be an improvement of movements and posture. Minor evidence of damage to the corticospinal tract, in the form of a positive Hoffman's sign or extensor plantar response but without any evidence of motor weakness, was present in one-third of the cases.

An accurate evaluation of the operative procedure on the globus pallidus is impossible at the present time for several reasons. First, the reports in the literature are for the most part too sketchy for the reader to determine the extent of the favorable (or unfavorable) results of the operation. With few exceptions, the reports have been con-

cerned mainly with the technic of operative procedures, with only a brief paragraph or two concerning the results. The results are usually expressed by such terms as "improvement" or "satisfactory" in a certain percentage of the cases. More complete description of the status of the patient preoperatively and at specific intervals after the operation is needed.

Secondly, there is no uniformity in the operative procedures. The approach to this region and the agents used for destruction of the globus pallidus or ansa lenticularis have varied, and it is doubtful whether the operative procedure of any one surgeon can be exactly duplicated by other surgeons.

Thirdly, there have not as yet been any reports of the histologic examination of the brains of operated patients which would make it possible to correlate the site and extent of the lesions with the clinical results.

Finally, the applicability of these operative procedures is limited to a small group of patients with predominately unilateral symptoms. The fear of serious untoward results has prevented most surgeons from destroying the globus pallidus on both sides.

Final evaluation must await perfection and standardization of operative technics and long-term observation of cases subjected to operation. Necropsy study of patients in whom alleviation of symptoms followed operative procedures should yield crucial information with regard to the pathophysiology of the symptoms of basal ganglia disease.

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■ E. H. Weber has shown, that in a part that has lost its skin, there is a loss of feeling cold, heat, and touch. Perhaps, however, it would be right to make an exception for the conductors of impressions of tickling, in the trunks of nerves, as a certain degree of pressure upon them gives a feeling of tickling that we refer to the periphery. But whatever may be admitted in regard to this fact, there is something concerning not only this kind of conductors, but also all the others, which seems quite certain. It is, that they all may acquire, particularly, if not exclusively, under the influence of inflammation, the power of being excitable, and of giving sensitive impressions which are referred to the periphery. This change may take place in all their length, from their terminal ramification in the different parts of the body, to their origin in different parts of the brain – i.e., in the branches and trunks of the nerves, in the gray matter of the spinal cord, in the medulla oblongata, the pons Varolii, and most of the other parts of the encephalon. This is true with respect to the conductors of the guiding muscular sensations, as also those of impressions of cold and heat, as well as the other kinds of conductors.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

Some Problems in the Pathology of Mental Deficiency with Microcephaly

Orville T. Bailey, M.D. and John S. Woodard, M.D.

MENTAL DEFICIENCY may be associated with so wide a range of lesions that a complete survey would cover a very large segment of pediatric neuropathology. In this paper, it is proposed to concentrate on nine patients whose mental deficiency was associated with microcephaly (table 1) and to discuss briefly for contrast four others in whom mental deficiency was associated with craniosynostosis (table 2).

For the purpose of the present discussion, microcephaly may be defined as a reduction in total brain mass, caused partly or entirely by arrest or retardation in growth of the brain. A reduction in brain bulk is by no means invariably associated with a small head, for fluid accumulations within or exterior to the brain may lead to the development of a skull which is normal in size or even abnormally large. While hydrocephalic brains may sometimes qualify under this definition, they are excluded from the present series.

Microcephalic brains tend to fall into two distinct groups. One group includes those in which growth disturbance is the sole factor apparent in gross and histologic studies. The defect may result merely in subnormal size of an otherwise fairly normal appearing brain as seen on gross examination (microcephalia vera), or it may result in focal regions of early growth arrest (schizencephalic microcephaly). In the other major group, the growth disturbance is combined with evidence of destruction in the brain parenchyma, such as gliosis, myelin defects, accumulations of free fat, encephalomalacia, neuron loss, secondary tract degenerations, and nuclear changes. "Encephaloclastic microcephaly" accurately describes this group.

In all cases, complete autopsies were performed and histologic studies made of visceral organs as well as of the brain. Staining methods used included hematoxylin-eosin, Nissl, Sudan black, Sudan IV, Weil's method for myelin, and occasionally other special stains as required. All normal values for brain weight in childhood were taken from Coppoletta and Wolbach.[1]

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TABLE 1
MICROCEPHALY

Case No.	Type of Microcephaly	Age	Sex	Weight Brain Gm.	Normal Weight for Age, Gm.*	Clinical Findings	Associated Malformations
1.	Microcephalia vera	3 yr.	M	720	1,141	Idiocy, spastic quadriplegia	None
2.	Microcephalia vera	5 yr.	F	780	1,237	Idiocy, spastic quadriplegia	Present
3.	Microcephalia vera	7 yr.	M	610	1,263	Idiocy, spastic quadriplegia, convulsions	Present
4.	Microcephalia vera	32 yr.	F	855	1,250	Severe mental deficiency, convulsions	None
5.	Schizencephaly	10 days	M	160	382	Clinical picture dominated by intestinal atresia	Present
6.	Encephaloclastic	16 mo.	F	310	1,010	Enlarged head, mental deficiency, blind	None
7.	Encephaloclastic	2 yr.	M	410	1,064	Idiocy, spastic quadriplegia, blind	None
8.	Encephaloclastic	2 yr.	M	390	1,064	Idiocy, spastic diplegia, convulsions	None
9.	Encephaloclastic	15 yr.	F	850	1,250	Idiocy, spastic quadriplegia following measles encephalitis in early childhood	None

*Values from Coppoletta and Wolbach,[1] except for those of cases 4 and 9, which are from Gray,[2] p. 784.

MICROCEPHALIA VERA

Four of the patients in the series had brains which, though greatly reduced in size, were otherwise little altered from the normal in outward appearance and in consistency (microcephalia vera). Data are given in table 1. The following case is a representative example:

Case 1. A white boy was the second child of normal parents. The mother was well throughout pregnancy and delivery was uneventful with cephalic presentation. The child was brought to the outpatient clinic at nine months of age. Up to then weight gain and feeding had been satisfactory. In the clinic he could not support his head when held by the shoulders and could not sit up. He could not grasp objects or follow moving objects with his eyes. From time to time the body would stiffen and the eyes turn up. On examination the occipitofrontal head circumference was 34 cm. The anterior fontanelle measured 1x2 cm. An external squint was noted in the left eye. Neurologic examination was negative. Roentgenograms showed normal bone age. In the electroencephalogram there were generalized slow waves and multiple spikes from both hemispheres. The child was cared for at home until the age of two years, when he was committed to Muscatatuck State School. While there he had spastic quadriplegia and opisthotonus. The mental status remained unchanged. Death occurred at the age of three years after a brief febrile episode.

Autopsy. The immediate cause of death was acute interstitial bronchopneumonia. Mild splenic fibrosis was the only other extracranial lesion.

The brain weighed 720 gm. (normal 1,141 gm.) and the occipitofrontal circumference was 37 cm. The calvarium was smoothly moulded to the cerebral contours and was not thickened. There were no abnormalities of the dura, leptomeninges, or surface blood vessels. While the general form of the brain was not grossly distorted except for its small size, sections made after fixation showed that the usual gross landmarks of the thalamus were absent and the entire neuraxis was small out of proportion to the rest of the brain. The regions of the dorsal thalamus and pulvinar were very small and glassy white. In contrast, the corpus striatum was normal in volume. In the cerebral hemispheres, the convolutions were small and complex in arrangement with sulci extending nearly to the corona radiata. Both superficial and deep white matter were much reduced.

On microscopic examination the relatively differentiated neurons of the neuraxis, such as those of the motor nuceli and the large neu-

TABLE 2
CRANIOSYNOSTOSIS

Case No.	Age	Sex	Wt. Brain Gm.	Cranial Abnormality	Brain Abnormality	Clinical Data
10	5 yr.	F	1,210	Turricephaly with closure of coronal and sagittal sutures. Digital impressions. Small body of sphenoid bone. Platybasia.	None	Mental deficiency, Mongolism
11	28 yr.	M	1,590	Dolichocephaly with closure of sagittal suture. Wide base of skull. Narrow sphenoid body. Platybasia.	Flattening of cerebral convolutions	Mental deficiency,
12	44 yr.	M	1,200	Turricephaly with closure of coronal and sagittal sutures. Wide skull base. Narrow sphenoid body. Digital impressions. Platybasia.	Atrophy of optic nerves and tracts	Mental deficiency,
13	63 yr.	M	1,320	Premature closure of all sutures. Symmetrical, small skull with wide base. Narrow sphenoid body.	None	Mental deficiency,

rons in nucleus gigantocellularis, were present but small and few. In contrast, the relatively undifferentiated neurons of the nucleus trigeminalis spinalis and the small neuron nuclei in the floor of the fourth ventricle appeared to be prolific, crowding and replacing adjacent structures. The inferior olivary nuclei were fairly well developed, although a few heterotopic islands of this nucleus were found among the internal arcuate fibers. The pontine nuclei contained rather immature neurons with reduction in the bundles of myelinated fibers. In the medial portion of the dorsal thalamus anteriorly was a group of moderately differentiated neurons fairly typical of those of the dorsomedian nucleus. Actual differentiation of the thalamic nuclei, however, was not present. Anteriorly the neurons became increasingly immature in appearance, merging with a mass of very undifferentiated cells in the anterior extremity of the thalamus. The pulvinar and lateral portion of the thalamus contained very few differentiated neurons. The pallidum contained typical neurons, although they seemed small and reduced in number. The small neurons of the striatum appeared almost normally differentiated. Heterotopic islands of these neurons in relation to the internal capsule were frequent. The entire cerebral cortex was markedly immature, although in most regions a suggestion of lamination could be seen and the cortical migration of neuroblasts appeared to be complete except in a few small areas. All cortical neurons appeared very immature, being small and round with a small amount of cytoplasm. Pyramidal neurons were rare. The cerebellum contained many small scattered defects in its mantle, often occurring only through the cortex on one side of a folium, but sometimes extending through the interfoliar white matter as well, leaving a single band of cortex without any supporting white matter. In the cerebellar cortex, large anomalous blood vessels usually replaced the usual capillary interfoliar vasculature.

This patient, as in cases 2, 3, and 4, had striking defects in cytoarchitectural development at all levels in spite of the fact that externally the brain appeared well formed but small. The essential defect seemed to lie in arrest of development in the neuron pattern. This arrest in most regions was at the stage where the migrated neurons begin the process of lateral expansion, which results in convolution formation.[3]

In occasional convolutions there was arrest at a still earlier stage, in which neuroblast migration was incomplete, resulting in a rather flat gyrus composed of diffusely distributed and primitive neurons. Instances in which this degree of developmental arrest was uniformly present throughout the cerebrum did not occur in the present series but have been recorded by others[4] as agyric microcephaly.

The small bulk of deep cerebral and convolutional white matter was largely

due to the paucity of more differentiated neuron forms in the cerebral cortex with resultant reduction in long fibers of the white matter.

That the defects in these patients are not confined to the cerebral cortex is shown by the incompletely developed cytoarchitecture of the dorsal thalamus and pulvinar. There was a striking deficiency of neuroblast migration, with regions with a few neuroblast clusters and heterotopic islets of small striatal neurons but with very few well-formed thalamic neurons. Focal defects were also found scattered throughout the cerebellar mantle.

The histologic study of these brains strongly suggested that the process is a dysgenetic one, an opinion held by others who have described similar cases.[3,4] Not only is there a picture of great immaturity in the cerebral cortex and elsewhere in the brain, but there is also no evidence of necrosis or retrograde processes. It is difficult to point to any precise moment in fetal life when the arrest occurred. Development may have ceased in different areas at different times from two to six months of fetal life. The chief defect seems to be a reduced capacity for neuron differentiation which affects the cerebrum and neuraxis. In the cerebellum, however, the process is much more focal.

Three of the four patients with microcephalia vera died in childhood after a clinical course characterized by idiocy and spastic quadriplegia (table 1). Such complex and disseminated abnormalities of so much of the brain could hardly be consistent with organized mental and motor functions. It is of interest, however, that microcephalia vera is compatible with adult life. Case 4 died at the age of 32 years after lifelong mental deficiency of severe degree.

Cases 2 and 3 each had several extraneural anomalies. In both, there was maldevelopment of the teeth and pinna of the ear. Case 2 also exhibited spina bifida occulta and precocious puberty. In case 3 there was bilateral cryptorchism and hypermobility of all joints. In all patients with microcephalia vera in this series there was some degree of cranial asymmetry in addition to small size. This has been regarded as the result of moulding to the abnormal brain.[5] While the presence of extraneural anomalies in a patient with microcephaly and severe mental deficiency offers collateral evidence of a dysgenetic process in the brain, it is not specific for microcephalia vera (compare case 5 in table 1).

SCHIZENCEPHALIC MICROCEPHALY

The term "schizencephaly" has been applied to the symmetric focal defects in cerebral and cerebellar mantles which are consistently found in association with multiple congenital anomalies within the central nervous system and also widely scattered throughout the remainder of the body.[6] These defects may be extreme, causing great reduction in brain mass, or they may consist merely of cleft-like abnormalities. Only in severe schizencephaly is the brain weight sufficiently reduced to justify the inclusion of these cases in the category of microcephaly.

On histologic examination of the membrane, one finds only primitive-appearing supportive tissue without evidence of further differentiation or destruction. While grossly the defects are sharp and surrounded by well-formed radiating gyri, microscopic sections may show a narrow zone of microgyria bordering the defect and other evidence of transitional

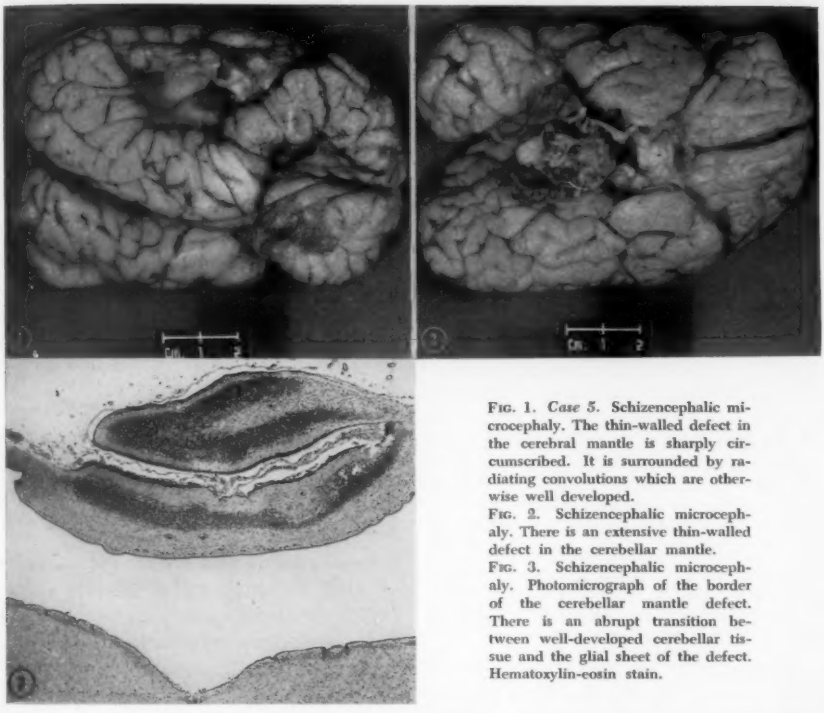

FIG. 1. *Case 5.* Schizencephalic microcephaly. The thin-walled defect in the cerebral mantle is sharply circumscribed. It is surrounded by radiating convolutions which are otherwise well developed.
FIG. 2. Schizencephalic microcephaly. There is an extensive thin-walled defect in the cerebellar mantle.
FIG. 3. Schizencephalic microcephaly. Photomicrograph of the border of the cerebellar mantle defect. There is an abrupt transition between well-developed cerebellar tissue and the glial sheet of the defect. Hematoxylin-eosin stain.

degrees of development. Also characteristic of the schizencephalic brain is the occurrence of many histologic vascular and parenchymal anomalies often scattered at random throughout the neuraxis and cerebellum.

Case 5. A white male infant was admitted to the Mary Imogene Bassett Hospital, Cooperstown, New York, at four days of age because of vomiting since birth. There were four normal siblings. The mother's pregnancy and delivery were normal. At laparotomy a single stenosis at the junction of the jejunum and ileum was found and an enteroenterostomy was performed. After a stormy course the infant died in respiratory failure on the fifth postoperative day, ten days after birth.

Anatomic diagnosis. Enteroenterostomy, recent; pulmonary atelectasis; patent foramen ovale; hydronephrosis, right.

The brain weighed 160 gm. (normal 382 gm.). The occipitofrontal head circumference was 31 cm. Roughly symmetric, bilateral defects in the cerebral mantle were present, following the lateral fissures on the convexities of the hemispheres. On the left the defect was a narrow cleft 1 cm. in width; on the right it was much larger, occupying about 40 per cent of the lateral aspects (figure 1). Smaller defects were present in the dorsal and medial surfaces of the frontal lobes. A smooth sheet of neural parenchyma replaced the cerebellar mantle, except for the anterior lobe which had its usual appearance (figure 2). The restiform bodies and middle cerebellar peduncles were represented only by very small bands of white matter. The olivary prominences were absent and the basis pontis small. On section the cerebral cortex was normal in width where it could be identified, but the diencephalon and deep cerebral gray matter were reduced.

On histologic examination the inferior olivary and pontine nuclei were absent. The cerebellar mantle defects showed abrupt transitions from normal cortex to a sheet of glial tissue associated with large, anomalous blood channels (figure 3). Similar circumscribed defects with anomalous vessels encroached on the dorsolateral portions of the medulla. The dorsal thalamus consisted of immature appearing neurons and the usual nuclei were not differentiated. In general the cerebral cortex was well laminated and contained well differentiated pyramidal neurons. As the defects in the cerebral mantle were approached, there was a rapid transition in the cerebral cortex to an immature state. First the small pyramidal neurons were replaced by granule-like neurons with little stainable cytoplasm, and then the internal granule layer disappeared, leaving a solid layer of primitive neurons. With this degree of immaturity, the convolutional formation exceeded the sulci, so that the molecular layers of adjacent convolutions were often continuous without the interposition of sulcus and leptomeninges. Upon reaching the membranous portion of the mantle defects, the leptomeninges contained increasing amounts of glial tissue and finally fused with the attenuated cerebral mantle to form one narrow band.

In this brain the most striking lesions were symmetric, circumscribed defects in both cerebral and cerebellar mantles. The lesions appeared to represent early focal arrest in development, with gradient stages of immaturity as the agenetic regions were approached. Further evidence for the developmental nature of the defects was found in a multiplicity of equally early deficiencies in the neuraxis. As in the instances of microcephalia vera in the series, the histologic findings were those of undifferentiation of neurons and nuclear groups rather than uncoordinated dysplasia or retrograde degenerations.

It would seem justified to include such instances as case 5 in the group of microcephaly as a dysgenetic process leading to greatly reduced brain mass. A comparison with microcephalia vera suggests that in schizencephalic microcephaly the developmental defects are the more focal and, within each focus, more complete from their inception.

In such instances as case 5, little can be determined in regard to the neurologic status of the patient because of the dominant clinical urgency of the extracranial anomalies. In some of the reported patients,[7] but not in case 5, one or more of the malformations led to obstructive hydrocephalus with ballooning of the cerebral hemispheres at the expense of the defects in the cerebral mantles. In such cases, transillumination of the head has on occasion allowed the superior sagittal sinus and the borders of the defect to be visualized.

ENCEPHALOCLASTIC MICROCEPHALY

Both microcephalia vera and schizencephalic microcephaly are fairly well defined pathologic entities in which there is evidence of retardation in the development of the brain without demonstrable tissue destruction. There remains, however, a group of microcephalic patients which is far more heterogeneous, the only common ground being the presence of tissue destruction as well as growth disturbance as factors in the reduction of brain mass (encephaloclastic microcephaly).

Destructive lesions in the central nervous system leading to encephaloclastic microcephaly are as many and as varied as are the causes of cerebral atrophy in adults. Any type of disease causing sufficient destruction of brain tissue before growth is completed may produce this type of microcephaly. The growth disturbance may result from perinatal disease, in which case it has few developmental implications. More often the

FIG. 4. *Case 6.* Encephaloclastic microcephaly. Roentgenogram following injection of air through parietal burr holes. The cranial vault is large in proportion to the face. Sufficient fluid has been displaced by air to show that the greater part of the cranial cavity is occupied by fluid.

FIG. 5. Encephaloclastic microcephaly. Brain viewed from above. The cerebral hemispheres are small and much distorted, while the cerebellum appears essentially normal.

destruction occurs in fetal life and results in a complex combination of developmental retardation with regressive changes. Four examples of this type of microcephaly are recorded in table 1. Two especially interesting patients are described in detail:

Case 6. A white female infant was brought to the hospital at four days of age because of an enlarged head. She was the first child of normal parents. Delivery was by breech presentation. On examination the occipitofrontal head circumference was 38.8 cm. and the anterior fontanelle measured 4x4 cm. No further abnormalities were found, spontaneous movement, tendon reflexes, and sensation being normal. No improvement was obtained from repeated subdural taps, which yielded small amounts of xanthochromic fluid. Bilateral burr holes were then made and the dura incised. Great quantities of clear fluid with a protein content of 429 mg. per cent were obtained, apparently from a massively enlarged subarachnoid space. Roentgenograms after air injection through the burr holes (figure 4) showed a large calvarium relative to the size of the face. A fluid level was demonstrated; by changes of position, the outlines of a small, maldeveloped brain were seen. The head size did not increase further, but her condition necessitated admission to Muscatatuck State School at nine months of age. There the patient appeared hydrocephalic and had difficulty in holding up her head. She cried a great deal and seemed totally blind. Death occurred at 16 months after a brief respiratory difficulty. No change in mental or neurologic status had been noted.

Autopsy. Anatomic diagnosis: Acute and chronic bronchopneumonia, bilateral, with abscess formation; acute pleuritis, bilateral.

The brain weighed 310 gm. (normal 1,010 gm.). The head was normal in size and the fontanelles closed. There was great thickening of the entire right side of the calvarium, while the left side was normal. The right side of the dura was 3 mm. thick and over the cerebral convexity contained a large cystic area 10 cm. in diameter containing white, semi-solid material. On the left the dura was completely split into two sheets, one of which followed the falx and closely invested the brain surface. The other was applied to the calvarium. On exposure of the brain, the cerebral hemispheres

were seen as small, irregular masses with fairly well defined temporal lobes. The rest of the cerebral tissue was composed of bizarre lobulations and sulci, with an extension of the right cerebral mantle to form a long, thin tube passing through the falx and into the left anterior cranial fossa (figure 5). Circumscribed areas of the cerebral cortex were deep brown, associated in some places with convolutional atrophy and in others with gelatinous degeneration. The only abnormality of the brainstem and cerebellum was reduction in size of the basis pontis and medullary pyramids. The pituitary and cranial base were normal. After fixation, sections showed the diencephalon to be small and poorly delineated. While the head of the caudate nucleus was well formed, the rest of this structure could not be identified. There was a complete defect in the cerebral mantle of the right parietal region, but elsewhere the cerebral cortex was 1.5 to 2.5 cm. in thickness.

On histologic examination there was secondary atrophy of the pyramidal tracts. The diencephalon contained regions of neuron degeneration and loss in contiguity with cerebral cortical lesions. The projecting nuclei of the thalamus were represented by glial masses without neurons. Most of the cerebral convolutions contained few nerve fibers and consisted almost entirely of glia with regions of microcyst formation, in which there were hemosiderin deposits and gitter cells containing stainable fat. In some very small convolutions, faint outlines of the molecular layer could be traced directly into areas of complete glial replacement. The fully developed hippocampal and dentate archicortex was dorsal to the corpus callosum. The histologic structure of the dura was that of loose-textured collagenous tissue. No dural sinuses could be identified. In their places, a few small to medium-sized veins coursed at widely spaced intervals through the dural connective tissue. There were numerous neuroglial rests in the leptomeninges.

Case 7. A colored boy manifested amentia and spastic quadriplegia from the time of birth. He took feedings poorly and had occasional generalized seizures. The pupils did not react to light and the patient appeared blind. No motor or intellectual progress was made. At the age of 19 months he was sent to Muscatatuck State School where he continued in much the same state and had repeated seizures. He died at the age of two years after a brief febrile episode.

Autopsy. Anatomic diagnoses: Acute bronchopneumonia; hirsutism, facial.

The brain weighed 410 gm. (normal 1,064 gm.). The calvarium was small and abnormally thick throughout. The dura was composed of a very thick, soft sheet of tissue with no recognizable dural sinuses. A greatly widened subarachnoid space was present. In the minute cerebral hemispheres, the convolutions were almost uniformly small and separated by wide sulci (figure 6). In a few areas, pigmented foci were found with convolutions about 1 mm. in width, each focus covering approximately 1 sq. cm. The pituitary fossa was shallow and the adenohypophysis absent. In contrast to the cerebrum, the brainstem and cerebellum were well formed and normal in size for the age of the patient, the only alteration being reduction of the basis pontis and pyramids. After fixation sections showed nearly symmetric cystic degeneration of the cerebral white matter, especially in the anterior portion (figure 7), as well as great convolutional atrophy, the gray matter measuring less than 1 mm. in width. There was atrophy of the thalamus and hypothalamus and cystic change in the lentiform nucleus. The corpus callosum was attenuated and the ventricles symmetrically enlarged in relation to the cerebral mass.

On histologic examination the brainstem and cerebellum were free from change other than secondary pyramidal tract degeneration. There was extensive cyst formation in the cerebral cortex, with replacement of neural tissue by glia throughout the white matter and in the basal ganglia. The dorsal thalamus was almost wholly composed of glia. Throughout the cerebral hemispheres, numerous gitter cells and deposits of hemosiderin were present. Cortical lamination was present and the smaller pyramidal neurons were well differentiated. However, the foci of very small convolutions were composed wholly of glia. A well defined molecular layer could be found up to the margins of such areas. There were occasional foci of calcification in the cerebral cortical tissue but not in blood vessels. The dura was composed of loose-textured connective tissue. No dural sinuses could be identified, only a few thin-walled and widely spaced blood channels being found in the places where dural sinuses would be expected.

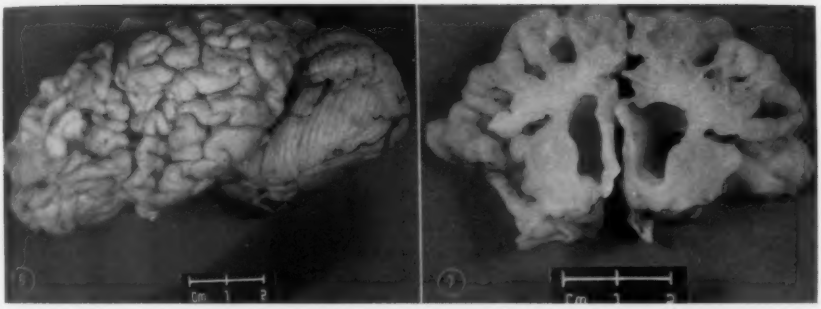

FIG. 6. *Case 7.* Encephaloclastic microcephaly. Lateral view of the brain, showing a small cerebrum and essentially normal cerebellum. The cerebral convolutions are small, especially toward the frontal pole.
FIG. 7. Encephaloclastic microcephaly. Coronal section through the frontal lobes, showing generalized atrophy with some cystic degeneration in the convolutional white matter.

Both of these cases belong to the form of encephaloclastic microcephaly. They show some similarity to cases discussed by Greenfield and Wolfsohn[3] as a complex microgyric type of microcephaly. They felt that the arrest in development of the cerebral cortex and white matter occurred at about the fifth month of fetal life. The disturbance in cortical architecture is at least partly due to neuron loss, since the molecular layer can often be followed into areas where neurons are few and gliosis is prominent. The presence of free fat in relation to blood vessels is further evidence of a regressive change in contradistinction to a developmental disorder.

On the other hand, the heterotopic cerebellar cortex in the midst of cerebral convolutions in case 8 indicates that altered propulsion may be combined with developmental retardation and regressive changes. The primary pathologic changes were restricted to the cerebrum. The cerebellum and the neuraxis showed only secondary tract and retrograde nuclear degenerations. The clinical problem in these patients was essentially that of idiocy or severe mental deficiency.

The nature of the disease responsible for the interference with brain development cannot be determined in cases 6, 7, and 8; in case 9 idiocy and spastic quadriplegia followed an attack of measles encephalitis in very early childhood. This case differs from the others in the group in being the result of an illness in the postnatal period, and therefore the interference in growth was purely that which might be expected in postnatal development.

In this type of microcephaly the size of the cranium may give little or no indication of the degree of microcephaly. As an illustration, the initial clinical problem in case 6 was thought to be one of hydrocephalus. The space between the calvarium and brain was occupied by great accumulations of fluid. Failure in cerebrospinal fluid absorption would seem a probable factor in the disproportion between the brain mass and cranial capacity, since the superior sagittal sinuses were absent in cases 6 and 7.

COMMENTS ON MICROCEPHALY

Instances of microcephaly in which precise etiologic factors can be determined are the exception in our present

state of knowledge. Those most easily accounted for are usually the result of perinatal disease. Some cases with congenital cerebral cystic degeneration which appear to result from birth anoxia may survive sufficiently long to manifest a growth defect in addition to destructive changes. Diseases during very early infancy such as encephalitis (case 9) may arrest only the final stages of brain growth. After the first year of age the brain is so near the adult stage of differentiation and mass that a disturbance in further growth can seldom be detected in the shadows of an atrophic process.

Most cases recognized as microcephaly result from prenatal disease, and here the assignment of etiologic factors is more complex. The microcephalic brains under consideration divided themselves readily into two basic groups depending on the presence or absence of significant parenchymal destructive processes superimposed upon the growth disturbance. Use of such terms as exogenous, endogenous, primary, or secondary seems seldom justified in the present state of knowledge. More descriptive terms such as "dysgenetic" and "encephaloclastic" would seem more satisfactory.

Most instances of microcephalia vera are clearly dysgenetic problems in pure form. Retardation in varying degrees are found throughout the brain. The capacity for neuronal differentiation and maturation is subnormal. The more highly differentiated long fiber neurons in the cerebral cortex and diencephalon do not develop; this is the primary factor responsible for the small brain size. On the other hand, less differentiated neurons such as the small neurons of the striatum and the neuraxis may develop quite well and appear prolific in proportion to adjacent structures. The outward form of these brains depends largely on the state in which cerebral development fails. If cortical neuroblasts are incompletely migrated, the "agyric" form results. If this migration has taken place, lateral expansion occurs and results in formation of convolutions which are often small in proportion to the cortical thickness because of the paucity of long nerve fibers. The white matter, while reduced, is in itself fairly typical in appearance and contains the usual pattern of nerve fibers. The widespread defect in more highly differentiated neuron types and the range of immaturity apparent in neurons and cytoarchitecture suggest that action of the pathologic agent may have been very early, regardless of the final developmental stages attained. Early embryonic disorder is further suggested by the relative frequency of multiple extraneural anomalies, especially in schizencephalic microcephaly. Such early disorder in development might suggest a germ plasm defect or an "endogenous" disease. Experimental studies prove, however, that this is not necessarily the case. Stage-specific anomalies, including microcephaly as well as dysplasias of viscera and skeleton, have been produced in rats by x-ray radiation of the embryo.[8]

Schizencephalic microcephaly, like microcephalia vera, appears to be a dysgenetic process originating relatively early in fetal life. From the neurohistologic point of view, however, the circumscribed cerebellar mantle defects are the only specific features in common. This lesion is not specific to either type of microcephaly, as it is found in a wide variety of other early developmental disorders. Elsewhere in the nervous system schizencephalic microcephaly is unique

and differs basically from microcephalia vera by producing multiple focal and complete symmetric defects in neuron cytoarchitecture and neuroblast migrations in their earliest stages of organization. The general capacity for neuron differentiation in itself does not seem impaired.

Encephaloclastic microcephaly can usually be differentiated from the dysgenetic type if a few principles are considered. This lesion, like cerebral atrophy, seldom affects all parts of the brain to the same degree. Lesions are usually focal or disseminated and the neural parenchyma, which is not involved in the lesion, differentiates completely. This demonstrates that neuronal differentiation in itself is not impaired as it is in microcephalia vera. Even within the encephaloclastic regions, neuronal differentiation is not the predominating difficulty. In a very small atrophic gyrus there may be good lamination and differentiation of pyramidal neurons. Glia may replace the white matter of a well-formed convolution with differentiated cortex. This does not correspond to any developmental stage. The glial replacement of neural parenchyma often leads to striking gross induration. Accumulations of free fat and hemosiderin may be extensive. Bizarre perversions of differentiation, such as the heterotopic island of cerebellar cortex in the cerebrum of case 8, are sometimes seen in the earlier encephaloclastic lesions. Cystic degenerations may be extensive. Teratologic considerations may fix the time of injury more precisely than in dysgenetic microcephaly, but this problem is usually complicated by continuation of neural differentiation along normal or abnormal lines after the injury.

Few generalizations can be made on etiology of encephaloclastic microcephaly of prenatal origin. Even the basic pathogenic factors are usually very obscure and a matter of speculation. The frequent complete and circumscribed localization of the primary pathologic changes to the forebrain and diencephalon is another unexplained phenomenon. This localization and lack of sparing of specific neuron types within the encephaloclastic region might suggest that local factors are at work. Blood vessels, however, seldom show definite primary changes. Absence of dural sinuses in cases 3 and 4 might conceivably account for the distribution of lesions, but is more likely a regressive change in itself. Other instances display the same changes in the same distribution with normal-appearing sinuses. Nowhere is the problem of cause and effect more perplexing than in relating vascular factors to these lesions. It seems likely that a state of circulatory impairment such as edema might involve the forebrain and lead to the localized tissue destruction. This condition might result from local vascular factors but more probably from such disturbances as anoxia and other general noxious conditions.

CRANIOSYNOSTOSIS

In the examples of microcephaly presented above, the skull was either moulded to an already small and malformed brain or was enlarged because of accumulation of fluid between the cranium and the brain surface. It might be interesting to contrast these findings with those of patients in whom the primary defect was in the skull, the brains being nearly normal in size.

One such condition is craniosynostosis, of which four examples have been stud-

FIG. 8. *Case 11.* Craniosynostosis. Lateral surface of the right frontal lobe with the leptomeninges partially stripped. The convolutions are flattened and the sulci relatively narrowed. No evidence of parenchymal disturbance is seen.

ied at autopsy (table 2). In each patient one or more cranial sutures closed prematurely and in case 13 all did so. The brain attains its adult size much before other viscera, increasing from 335 gm. at birth to 1,042 gm. at 18 months.[1] If there is not room for the expansion of the brain during this period, the active growth of the brain is compressed (figure 8) and progressive mental impairment, blindness, strabismus, and other neurologic abnormalities result.

A representative example is as follows:

Case 12. A 43 year old white man had spent his life since early childhood in mental institutions because of severe mental deficiency and progressive loss of vision from youth. His entire family were feeble-minded. Death occurred after an attack of severe diarrhea.

Autopsy. Anatomic diagnosis: Acute bronchopneumonia, bilateral; acute colitis; corneal opacities, bilateral, mild.

The brain weighed 1,200 gm. The skull was turricephalic. On the interior of the calvarium there were deep digital impressions which closely followed the detail of individual convolutions. The brain filled the intracranial cavity to an unusual degree. There was marked reduction in bulk of the optic nerves and tracts. Some erosion of the body of the sphenoid bone was found, especially in the thin, delicate dorsum sellae. Platybasia was present with a basal angle of 160 degrees. No further changes were found after fixation. On histologic examination the only abnormality encountered was optic atrophy with extensive loss of nerve fibers.

In this group of patients, the premature closure of sutures resulted in a skull too small to accommodate a brain of normal size (or in case 11, greater than normal). At autopsy there was a wide range of irregularities in the form of the cranial vault, depending on the sutures prematurely closed. Much more consistent were secondary changes in the cranial base as the result of continued enlargement of the growing brain. These included enlargement of the base in all diameters, platybasia, and narrowing of the body of the sphenoid bone, sometimes with erosion.

Emphasis should be placed on the fact that craniosynostosis occurs in conjunction with a brain which is usually normal except for the effects of compression. That the brain of a patient with craniosynostosis is sometimes the site of concomitant disease is illustrated by case 10,

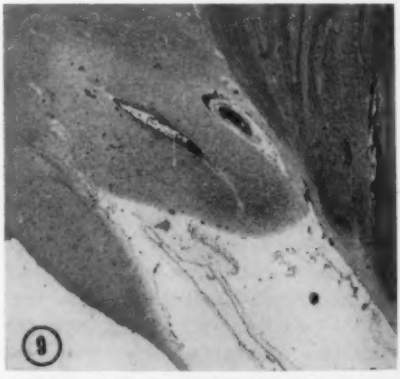

FIG. 9. *Case 12.* Craniosynostosis. A section through the optic tract in a Sudan black preparation. The atrophy of the optic tract is almost complete, the only preserved myelin sheaths being in the ventromedial portion.

a patient with mongolism in addition to turricephaly.

The compression effects on the brain, when of sufficient duration, lead to mental deficiency and blindness. While direct involvement of the optic nerves by the skull deformity can be demonstrated in those patients who become blind (case 11), the mechanism by which mental deficiency occurs is obscure.

Ingraham, Alexander, and Matson[9] have shown conclusively from the clinical point of view that early operative opening of sutures prematurely closed will allow the brain to develop normally. The four patients described pathologically in this paper illustrate the consequences of craniosynostosis when not surgically relieved. This, then, is one of the forms of mental deficiency which can be successfully treated, except in the occasional case in whom a cerebral defect occurs coincidentally.

Craniosynostosis is probably an inherent defect of the germ plasm,[10] as indicated by its high familial incidence, its predominant occurrence in males, and the frequent appearance of associated extraneural anomalies. That the premature closure of the sutures is the result of a stimulus continued over a long period of time is shown by the rapid reclosure of operatively opened sutures unless special materials are placed in the incision in the bone so as to prevent refusion.[11]

SUMMARY

Nine cases of microcephaly studied at autopsy are described. These were divided as follows:

Microcephalia vera (four cases) is a disseminated dysgenetic process resulting in a miniature brain which resembles the normal externally except in size but is the seat of complex defects in neuron differentiation.

Schizencephalic microcephaly (one case) is a focal dysgenetic process resulting in focal cerebral and cerebellar mantle defects and defects in the neuraxis.

Encephaloclastic microcephaly (four cases) is the result of regressive changes occurring in fetal or perinatal life. There is usually a complex mixture of tissue destruction and growth disturbances occasioned by the retrograde processes.

All types of microcephaly were associated with severe mental deficiency.

The skull is moulded to the cranial contents and is not primarily affected when there is reduction of head size.

As a contrast to microcephaly, four mentally deficient patients with unrelieved craniosynostosis were described. Except in one patient with coincident mongolism, the anatomic changes were those caused by pressure of a deformed skull on a developing brain of essentially normal size and structure. This emphasizes the importance of early operation in craniosynostosis.

We wish to express our thanks to Dr. C. Van Z. Hawn of the Mary Imogene Bassett Hospital of Cooperstown, New York, for permission to include case 5, and to Mr. Alfred Sasser, Jr. and Dr. Hans Meyer of Muscatatuck State School for encouragement and many courtesies.

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■ I have found that a convulsive affection, very much resembling epilepsy, may be produced in animals. A few weeks after certain injuries to the spinal cord, in the dorsal or the lumbar region, especially in guinea pigs, fits appear spontaneously several times a day, or, at least, once every two or three days. But the most interesting point is, that it is possible to produce a fit when we choose, by simply pinching a certain part of the skin. These fits consist in clonic convulsions of almost all the muscles of the head, the trunk, and the limbs, except those muscles which are paralyzed. The animal seems to have lost its consciousness, or at least, its sensibility. There is an evident laryngismus in the beginning of the fit, and, after it, when it has lasted long, a state of drowsiness or unwillingness to move. I have ascertained that one part only of the skin has the power of producing the fit, and this part is that which covers the angle of the lower jaw, and extends from thence to the eye, the ear, and nearly to the shoulder. It is only the skin that has the power of generating the fit, as even the three nerves that send filaments to this part of the skin can be irritated without the occurrence of convulsions.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

On the Broadening Concepts of Neurology

I. S. Wechsler, M.D.

I DEEM IT a happy occasion to recall some of the important contributions of the man in whose memory the Hughlings Jackson Lecture is given, and to draw inspiration from one of the greatest masters in neurology. Hughlings Jackson is remembered for his profound observations and meticulousness as a clinician and for his philosophic insight into the functions of the brain. He possessed almost uncanny prescience in the days when the advanced knowledge of the structure and function of the brain we possess today was not available to him. He was gifted with the capacity to think beyond the facts, to deduce general laws or theories, and to propound concepts which have stood the test of time. It is a great tribute to the enduring worth of his ideas that after more than two generations since he enunciated his general principles they still continue to throw light on brain function and to inspire investigators. And so it is particularly fitting at this time, when clinical neurology has entered a new phase, to seek guidance from the philosophy which has so deeply enriched neurologic thinking.

As a clinical neurologist I am somewhat reluctant to speak on the philosophy of neurology and on the need of broadening concepts. But I am encouraged to say a few words on the subject because of the imperative necessity of ever bearing in mind the importance of theoretical generalizations and of a philosophic approach to neurology. Without the capacity to formulate theories, to invoke general principles, to correlate isolated data, and to draw logical conclusions based on verified observations, there can be no scientific medicine at all. Hughlings Jackson was aware of this, as are most scientific physicians today, and when he spoke of the theory of levels and applied the concept of evolution and dissolution promulgated by Herbert Spencer, he sought to give meaning to isolated clinical manifestations.

This is not a very novel or revolutionary proposition but it seems opportune to repeat old truths now that clinical neurology is being enriched by scientific research and by more direct studies on man in health and disease. For man is the most important experimental animal, the study of whom promises more direct and less inferential knowledge than is vouchsafed by study of lower animals. The cooperation of the neurologist, the neurosurgeon, the neurophysiologist, the

The Hughlings Jackson Annual Lecture, delivered May 9, 1956 at the Montreal Neurological Institute.

pathologist, the biochemist, the pharmacologist, the psychiatrist, the psychologist, scientists all, holds out great promise. To the faint of heart who naively foretell the disappearance of the clinical specialty, and with it the neurologist, the comforting assurance may be given that the report of the early demise is grossly exaggerated. It is true that the era of clinical classification, so brilliantly accomplished by men of genius, has largely come to an end. Many workers in their own fields have contributed to the growth of neurology. The neurologist and psychiatrist have contributed to neuroanatomy, the neuroanatomist and the neurosurgeon to neurophysiology, the neurophysiologist to the understanding of brain function, the neurologist to clinical medicine. Each plowed his own field; all enriched the discipline.

Before proceeding with clinical material in illustration of the special topic under discussion, may I digress for a moment to say a word about philosophy in general. Bertrand Russell once defined philosophy or much that passes for philosophy as the concoction of plausible reason for useful error. As generally understood, philsophy embraces logic, epistemology, and metaphysics. The scientist deals only with the first two and rejects the third. He cannot and must not engage in metaphysical speculation as doctors of old often did. Theory based on knowledge is indispensable for scientific method, for without it there can be no science at all. Thus stated, the philosophy which deals with generalizations furnishes the capacity to discover new relationships hitherto unobserved or unknown. Metaphysics is concerned with speculation largely divorced from experience and reality, with what is magniloquently called *á priori* knowledge, and with the notion of *sub specie æternitatis*. Indeed one detects in metaphysics much that partakes of schizophrenic thinking. Metaphysics has always impressed me as glorified scholasticism. It is no slander to state that both have retarded knowledge. There is a philosophy of science and a science of philosophy; there is no science of metaphysics.

Medicine like other scientific disciplines has long indulged the human failing to bridge with fanciful thinking or metaphysical speculation gaps in knowledge which scientific facts could not fill and to build systems with pseudophilosophical concepts which gave the illusion of knowledge that did not exist. Etymologically the word metaphysics means after or beyond physics, which covers a vast amount of ignorance. One may reasonably wonder just what kind of physics exists or can exist beyond physics. The delusively impressive phrase "transcendental reason" does even more grievous violence to critical reason and logic. What, one may ask, transcends reason, and how can reason comprehend whatever it is that transcends it? And so with the recent deceptive notion of extrasensory perception, one may also wonder and ask what is perceived and how can it be perceived by senses which cannot perceive. Now existentialism parades as a new metaphysic, which is so profound as to confound reason with words and to elude comprehension.

More relevant to our discussion is the word metapsychology, so beloved of certain types of mind, which once more raises the question of what is that psychology which exists after and beyond psychology, and how can normal psychologic thinking deal with what is beyond it. The scientific philosopher rejects the claim that one can take out a patent on

knowledge or a copyright on truth. He does, as he must, put forth theories based on observed facts, but he is fully aware that these are theories and is ready to discard them if convinced by unassailable evidence. It seems to me more profitable to follow Bacon and Locke and Hume and Auguste Comte, all of whom were superciliously disdained by metaphysicians as not being philosophers, than to follow Hegel who turned out to be a false philosopher and became the high priest of totalitarianism. Quite clearly, the scientific thinker does not and cannot speak in terms of eternal verities. For unless this is constantly borne in mind, there is the danger long ago pointed out by Thomas Huxley that truths which begin as heresies often end as superstitions.

Most of the original clinical observations and contributions made by neurologists and neuropathologists during the era of classification, important as they were, consisted largely of facts in themselves considerably isolated. Our forebears correlated their observations with focal brain lesions, with such anatomy and pathology and physiology as they knew, described signs and symptoms, grouped them into diseases or syndromes, and gave them diagnostic labels. Very often the isolated lesions were studied without reference to general brain function. There were honorable exceptions among the pioneers. Some neurologists drew fanciful schemata, often figments of the imagination, which were not rooted in definite knowledge and had little relation to reality. Some of the schemata of specialized geographic regions of the brain, of the anatomic organization of isolated brain functions, of extrapyramidal systems, and of the varieties of aphasia are good examples.

The fallacious concepts of silent areas of the brain which held sway for a long time have now given way to the recognition that there are no silent areas. The reason for designating areas as silent obviously lay in want of precise knowledge of the finer structures of the brain, of their anatomic connections, and their physiologic functions. Clearly, it is not the brain which is silent, but the neurologist and the anatomist and the physiologist who were and in large measure still are. We projected our silence, our own lack of knowledge, onto the brain. To this could be added the error of interpreting as positive negative evidence of brain lesions and of attributing positive function to destroyed areas. Increasing knowledge of the function of the parietal lobes and the growing realization that both hemispheres have to do with general brain function are examples of the broadening concepts.

Though largely discarded, the word degeneration is still employed to describe disappearance of ganglion cells and axis cylinders, the meaning of which and the causes of which wholly escape us. Sclerosis is another term which designates disappearance of nerve cells and fibers and their replacement with glial tissue without vouchsafing information as to etiology. Both terms represent final end products and are in effect necropsy diagnoses in vivo. The word demyelination, although a little more descriptive, is not yet an ultimate answer. What is perhaps more important is the realization that there is a selective affinity of noxious agents for specialized structures of the brain. The conjecture is warranted that the chemical composition of the agent and the varying chemical constitution of brain tissues determine the selectivity of the one by the other. This

may explain, for example, why manganese may seek out the globus pallidus, why carbon monoxide affects selectively certain nerve cells and fibers, why copper appears to have affinity for the lenticular nucleus, why a virus selects the substantia nigra, why some noxious agents have a predilection for white matter, or how a vitamin deficiency is the general underlying factor in many neuropathies previously called neuritides and attributed to a variety of causative agents. All of this does not contradict the important generic fact that the location of a lesion determines the clinical picture to a greater extent than the nature of the lesion. For example, injury of the pyramidal tract, whether it be the result of trauma, of vascular diseases, of a neoplasm, of infection, of demyelination, or of any other noxious agent, will result in the same well-known signs and symptoms even though the onset, the rate of progress, the prognosis, and the treatment may vary.

The concept of irreversibility, too, is beginning to lose its old meaning, considering that BAL, for example, can reverse to some extent a seemingly fixed process in lenticular disease or a mixture of carbon dioxide and oxygen can temporarily reverse a catatonic process of long duration. We used to speak of dementia precox as an entity, despite the fact that in large numbers of cases there was no true dementia and many were not precox. Now the high-sounding Greek word schizophrenia, which simply means splitting of the mind, has replaced the discarded label without adding much to fundamental knowledge. Worse still, it ignores what is becoming increasingly evident, that schizophrenia is not a single disease entity but that there are three or possibly four syndromes of quite different etiology. Multiple sclerosis also eludes our knowledge of cause and therefore of effective treatment, despite the loud fanfare and the somewhat dubious publicity. Here, too, we are not dealing with one disease but with three or four similar clinical syndromes of varying etiology. And so with amyotrophic lateral sclerosis, other amyotrophies, the dystrophies, the migraines, and some others.

Psychiatry, too, is in urgent need of broadening, or perhaps narrowing, of concepts. Take the phrase total organism or the term holism. On logical analysis we find a truism or a platitude which seeks to tell everything and succeeds in telling nothing. It reminds one of the expression "fluid of life" for blood, a beautiful poetic metaphor which became meaningful only when it was learned that there are red and white cells, and platelets, and hemoglobin, and oxygen, and sugar, and other components. It is becoming more and more evident that many psychiatric states are definite manifestations of pathophysiologically disturbed brain functions. Because of the complexity of the problem, we do not as yet possess a true psychiatric classification, the first desideratum of a scientific discipline. And so we use terms which do not adequately define symptoms and often delude ourselves in the vain belief that to coin a word is to create a fact. We hardly know what an idea is. All this because it is not yet possible to speak of psychologic processes in physiologic terms or of physiologic processes in psychologic terms. We use language which is the best tool of intelligent or conscious behavior and expression. But while language is our finest tool, it can also be a treacherous one, and one must learn to be its master, not its slave.

Unfortunately, metaphysical or metapsychologic thinking, though with lessening influence, still colors the study of the "mind"—by now a fairly discarded term. It is not too late, however, even at this date, to recall the modest pronouncement of Kant that the philosopher is better able than the physician to understand and to treat disease of the mind and the categorical dictum of Heinroth that sin is the cause of insanity and repentance its cure.

With the increasing realization that much of what is called mental disease is the expression of brain dysfunction, the conviction is growing that psychiatry and neurology are fundamentally allied and that the art is rapidly becoming a science. The contributions of Penfield and Rasmussen and Jasper and Bender are very important in this connection. Edwin Weinstein's studies of anosognosia in organic disease of the brain and his correlation of the symptoms with developmental and environmental personality characteristics are another straw in the wind. Louis Linn's tentative correlation of the ascending activating reticular system with the psychologic problem primarily associated with the mechanism of defense is also very suggestive. Hughlings Jackson's theory of anatomic levels and his concept of evolution and dissolution could perhaps be fruitfully applied to psychiatry as it has been to neurology. Experimental psychology has become indispensable in the study of neurology and psychiatry and is making important scientific contributions now that it has advanced beyond the limitations of academic psychology and the important but purely theoretical psychology of motivation.

In a recent essay on the meaning of consciousness, the argument was emphasized that consciousness is not a special faculty or entity which exists by itself, that there is not a single state of consciousness but that there are many and varying degrees or states of consciousness, and that we are dealing with a relative concept expressive of various relations. Not being a single entity existing of and by itself, one cannot speak of a seat of consciousness, localizable in any particular part of the brain. There are regions, acting perhaps as links in a chain of feed-back mechanisms, such as the hypothalamus, the centrencephalic system, the corticofugal projections of the brain, and the ascending activating reticular system, which have to do with consciousness and even challenge the supremacy of the cortex. That we generally think as we feel and not feel as we think may have some pertinence in this connection. As a corollary, the conclusion is justified that unconsciousness also is not an entity, that there are varying degrees or states of unconsciousness, that we speak essentially of a negative state expressive of absence of conscious awareness, and therefore is equally unlocalizable. To anthropomorphise a negative state and make it physiologically and psychologically operative is to do violence to logic, to all that is known of brain structure and function, and to the fundamental concept of Hughlings Jackson. As a pure verbal psychologic term, as a *facon de parler*, the use of the word unconscious is necessary and useful; as a physiologic scientific concept it has no validity.

It is with a feeling of hesitancy that I touch on the problem of epilepsy. To speak of it at the Montreal Institute of Neurology, where so many original and important contributions to the subject have been made, is somewhat rash and

literally like bringing coals to Newcastle. But may I venture the opinion that the word epilepsy has also lost its connotation as an entity? To begin with, we are dealing with a symptom and not a disease. The Greek word means seizure or fit, and to speak of an epileptic fit is to indulge in tautology. The symptom is of great complexity, varies extremely in expression, and even more perhaps in etiology. If conceived in terms of neural discharge, it is projected from or initiated and propagated by regions of the brain of various localizations. Thanks to the work of Penfield we can point to the localization of auras, of diencephalic fits, of psychomotor phenomena, of speech and voice discharges, of dream states, of *déjà vu* phenomena, and so on. But what of pancreatic adenomas, of other hypoglycemic states, of the carotid sinus syndrome, of heart block, of cerebral anemia, of uremic states, of allergic phenomena, all of which can cause convulsions? It seems to me that we are now in a position either to limit strictly the use of the word epilepsy or to discard it altogether and speak of the convulsive state. It broadens the concept, more accurately expresses present knowledge, and does away with the stigma, unjustified as it is, which attaches to the word epilepsy.

The intimate relationship of neurology to internal medicine has led some enterprising souls to put forth the modest claim that neurology, perhaps the most scientific of medical disciplines, which lends itself best to the correlation of signs and symptoms with anatomy and physiology and pathology, is a branch of internal medicine. Obviously neurology is a part of medicine in the sense that pediatrics and surgery and physiology and ophthalmology are. In his own grandiose moments, the neurologist could with more cogency speak of internal medicine as a branch of neurology. One need merely allude to the numerous medical syndromes that result from brain dysfunction, more particularly of the hypothalamic region. A type of coma formerly called vigil appears to be the result of involvement of the hypothalamus. In that small structure, weighing about four grams, are locked many secrets of general medicine: control of water, sugar, and possibly fat metabolism, regulation of pulse and respiratory rate, of blood pressure and temperature, of sex function, of states of consciousness, of elation and depression. So-called fever of unknown origin, which is no diagnosis at all, probably is hypothalamic in nature. It is not characterized by the usual concomitants of fever, such as leukocytosis, heightened sedimentation rate, sweating, and rise in pulse rate, and does not respond to the usual antipyretics.

Many years ago I called attention to the rare occurrence of abdominal syndromes resulting from disease of the brain and cited several illustrative cases. One was that of a boy who seemed to have had a typical attack of appendicitis and was operated upon for what turned out to be a normal appendix. He had a frontal epidural abscess. Another patient had classical attacks of renal colic which cleared up after successful removal of bilateral subdural hematomas. He had no renal calculi. A third was treated for duodenal ulcer which he did not have, all the while suffering from a cerebellar hemangioma. A fourth suffered from abdominal cramps and repeated episodes of urinary retention, diagnosed as hysteria; she had a glioma of the upper brainstem. In addition, one could men-

tion rare gastric perforation in tumors of the brain, occasional intussusception in experimental ablation of the cerebral cortex, so-called abdominal migraine, gastric auras, cramps and incontinence in acute panic, and abdominal symptoms in hysterics.

And now a word on slogans in neurology and psychiatry. I am alluding to the highly pretentious and ubiquitous term psychosomatic, which has seized the medical profession with something like furor. Clearly, slogans are not rooted in logic or reason, are always emotionally conditioned, and have no place in medicine. At best, psychosomatics is a point of view and is neither a science nor a medical specialty. There is a kernel of truth hidden somewhere in the theoretical concept, and maybe the kernel will sprout into a fruitful tree. For the present the word is a palatable cliché and a useful sop to ignorance. Somatopsychic is closer to neurology and general medicine, as the following case may illustrate:

A young man was brought to the office with the complaint that he showed grave moral lapses, spoke unclearly, had memory impairment, flung about his right arm uncontrollably, and suffered from peculiar attacks of slumping into temporary unconsciousness, during which he had bizarre minor convulsions. I was informed that he was being treated for Buerger's disease with intravenous saline injections. Examination revealed considerable dysarthria, some disorientation, hemiballism, highly pigmented buccal mucous membrane, and hypotension. He evidently showed signs of Addison's disease, which, unknown to the referring physician, was helped by the saline injections given for the thromboangiitis obliterans. The nature of the unconscious attacks was reminiscent of hypoglycemic seizures. The hemiballism, I thought, could be explained by a lesion in the body of Luys caused by vascular disease comparable to that involving the peripheral blood vessels. On admission to the neurologic service of the hospital, hypoglycemia was found and the electroencephalogram showed typical convulsive patterns. Before pursuing further studies, the patient was given large quantities of sweetened orange juice. The speech improved, the mental state cleared perceptibly, the hemiballism was almost abolished, and the abnormal electroencephalogram reverted to normal. Soon the oral administration of sugar ceased to have effect and he was given intravenous glucose. Again the symptoms began to clear and the electroencephalogram correlated well with the clinical improvement. But this favorable result also lasted only a few days. Apparently the brain could not utilize the sugar. Examination of the blood showed very high pyruvate content, indicating failure of complete breakdown of sugar for utilization by the brain. Thiamine chloride was administered for its coenzyme properties, the pyruvate blood content dropped rapidly, the clinical symptoms receded, and the cerebral dysrhythmia became much less abnormal. This is not the whole story; the case is here recorded in very condensed fashion as an illustration of the relationship of internal medicine to neurology.

Before concluding, I should like to cull a few words from a paper on S. Weir Mitchell on my conception of a neurologist. "It has always seemed to me that the great neurologist, like other great doctors, should be a little more than a specialist in his own field. Clearly the neurologist must be complete master of

clinical neurology and have thorough grounding in neuroanatomy, neurophysiology, and neuropathology. He should have sound acquaintance with internal medicine and possess deep insight into psychiatric states. One simply cannot be a well-rounded clinical neurologist unless one is also a good psychiatrist, and it is not possible to practice the one without knowledge of the other. Whereas many psychiatrists, much to the detriment of progress, I believe, appear to have little interest in the structure and function of the brain, the practicing neurologist does not share this major disdain or the cavalier approach. The eminent neurologist should also be a scholarly doctor with genuine love of literature, including the great classics of all times, and have a live interest in general history. Without an historical perspective, it may be added, there can be no culture at all. If, in addition, the neurologist be a man of wisdom and understanding with warm insight into human foibles and human folly and possesses the sense of humor which enables a man to laugh at himself, the desiderata for eminence are possible of fulfillment."

And now I shall conclude by quoting the final paragraph of my *Introduction to the History of Neurology* written more than 20 years ago. "To the neurologist the study of the growth and development of neurology is as thrilling as it is fascinating. The struggles which the early observers and investigators went through, the errors which they made, the blind alleys in which they wandered, and the spirit of adventure which animated them can only instruct, challenge, and inspire. But the story is by no means ended; indeed it has just begun. Knowledge of the structure of the nervous system is far from complete; its functions are but dimly understood. Neurophysiology is still an infant just beginning to toddle and walk; biochemistry and biophysics are not even fledgelings out of their shells. They are mistaken who think that there can be ultimate understanding of mental processes without fundamental knowledge of the function of the brain. Adventure still beckons to the pioneer in neurology, and glory and honor no less than inner rewards await the coming investigators. It is trenching neither on folly nor on prophesy to venture the prediction that neurology has a great future. Others will no doubt record more fully the old epochs and the new. This meager history merely seeks to honor in the telling the men who by their struggles and achievements have built the house of neurology in which we now live."

Shift to Older Age Distribution in Parkinsonism

A Report on 1,000 Patients Covering the Past Decade from Three Centers

Robert S. Schwab, M.D., Lewis J. Doshay, M.D., Hugh Garland, M.D., Peter Bradshaw, M.D., Eleanor Garvey and Betty Crawford

In October 1955, during the preparation of a report on the most useful drugs available in the treatment of parkinsonism, a surprising shift in the use of solenacious drugs was encountered from Artane useful in 1948 to emphasis on Parsidol in 1955. In looking for a possible explanation of the down-grading of atropine-like substances in use in our 400 patients, both private and those from an outpatient clinic devoted to parkinsonism, we surveyed the age factor. Since all of our material at the present time is on Kardex, the date of the patient's birth, date of first symptom of the disease, as well as a complete summary of all the treatment given in the years under our control, were available for study of the age distribution of patients in 1948 and 1955. For the 1948 group we selected patients who were seen either in the clinic or in private practice during that year. The total number of such patients was 252. These were then grouped according to age in decades (table 1). This shows a clear peak between 50 and 59 years.

The 1955 population of parkinsonism at the Massachusetts General Hospital was 331 patients. These were grouped in decades and showed a peak between 60 and 69 years, in contrast to those of 1948 (table 2). This finding, which is difficult to explain, was reported before the Boston Society of Neurology and Psychiatry in 1955.[1] During the discussion of the paper, this finding was commented on as possibly due to natural selection of older patients as the physician himself grew older. The possibility was mentioned that the outpatient group might be different from the private

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Read at the eighth annual meeting of the American Academy of Neurology, St. Louis, April 28, 1956.

TABLE 1
252 PATIENTS. AGE IN 1948

Under 29	30 to 39	40 to 49	50 to 59	60 to 69	Over to 70
			77		
		63			
				53	
	43				
10					
					7

TABLE 2
331 PATIENTS. AGE IN 1955

Under 29	30 to 39	40 to 49	50 to 59	60 to 69	Over to 70
				114	
			82		
					59
		48			
	28				
0					

group. Further comment was made that the population as a whole is living longer at the present time than in 1948, and this might affect the distribution curve.

As a result of this preliminary paper, it was decided to enlarge the series by requesting the collaboration of the chief of the Parkinson Clinic at N.Y. Neurological Institute and a neurologist in Leeds, England. They agreed to supply the necessary information in order to determine what result would be obtained from a larger series when plotted in this manner. During the collection of data on this larger series, efforts were made to obtain the type of initial symptom that the patient complained of when his disease began, and also whether or not there was a history of Spanish influenza or encephalitis during the epidemic of 1917 through 1926.

There were five categories of initial symptoms: 1) tremor, 2) rigidity and/or stiffness, 3) impairment in motor function of the limbs, such as loss of skill in typewriting, difficulty with handwriting, or difficulty with gait, 4) a group of general and diffuse complaints such as general fatigability, depression, general slowness in motor activity, inability to continue occupation, and so on, and 5) miscellaneous symptoms, including oculogyric crisis as an initial symptom.

Late in February 1956 the material was in our hands for analysis and interpretation. We increased our 1955 distribution list in these three centers to 1,147 and the 1948 population group to 466. Data about the type of initial symptom according to the five categories mentioned above were obtained on 800 patients, since in many situations the early clinical records for the 1948 population had been destroyed. Satisfactory and accurate information about the date of onset of the disease as well as the date of birth was obtained in 818 patients of the total.

Since the shift in age distribution curves in our original Boston material presented in November 1955 showed two similar curves seven years apart, a suggestion was made that this might lead to the conclusion that the parkinsonism population was growing older as a group and therefore might point to a common infectious process as the etiologic factor in a large percentage of patients. With this in mind, our consultant suggested that we make a graph of the number of patients whose disease began in unit years after positive history of influenza or encephalitis. In those patients who

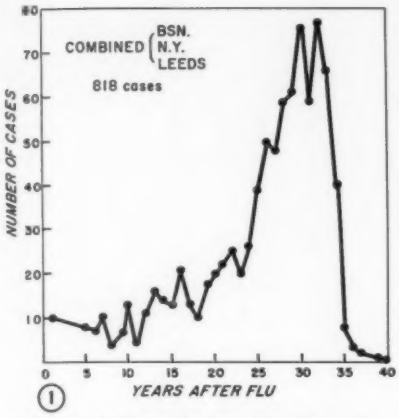


FIG. 1. Relation of the number of patients in 818 cases of parkinsonism according to the number of years after the history of influenza or encephalitis during the epidemic of 1917 to 1926. An arbitrary year—1920—was taken for those who did not recall any such illness.

could not recollect any such illness in the epidemic period from 1917 to 1926, or where there was no history in the record of such a condition, an arbitrary average date of 1920 was selected for this purpose. When this data was plotted, a surprising peak in the curve was shown (figure 1). The total of 818 patients were arranged according to the number of years between their flu exposure and the onset of their symptoms. Actually, but not shown in this curve, the individual groups in Boston, New York, and Leeds all showed similar curves with peaks in the same place. It is to be seen that, although there is a gradual rise to the peak on the left side of the curve, there is an abrupt fall on the right side. Seventy-one per cent of the total group fell within this peak between the periods of 25 through 34 years after their alleged exposure to influenza. The abrupt fall on the peak of the right hand of the curve may well be due to the fact that some patients whose symptoms began in 1954 and 1955, and even 1956, have not yet been in contact with us. We were able to determine in the 818 patients the length of time between onset and contact with our three groups; 48 were seen within a year of onset, 102 within the first and second year, and 130 between the second and third years. Since our three groups together average 100 additional patients per year, our calculated 1954 and 1955 onset values should be (if there was no fall-off of new cases) 50 and 20 patients, but the actual figures are 30 for 1954 and only five for 1955. This helps confirm the validity of our figures. In another two years, however, we should be able to determine whether this abrupt fall is a true value or an artefact. It is pointed out that the ten-year period embracing this peak covers approximately the same span in years as the duration of the influenza epidemic which we are considering as a possible cause in the majority of patients with this disease.

Another method of handling these data was to graph 818 patients according to their date of birth along the bottom line, and the date of onset of initial symptoms along the left hand vertical line. In the original curve, which cannot be shown here because it contains color points, each patient was given a point on the graph, and the three groups in Boston, New York, and Leeds were assigned different colors. This graph showed a strong concentration of points similar for all three groups, in fact, so identical in all three groups that one could not find any difference; 67 per cent of the total fell between the years 1945 and 1954 inclusive. This is in good agreement with the other graphs previously mentioned and again suggests a

TABLE 3

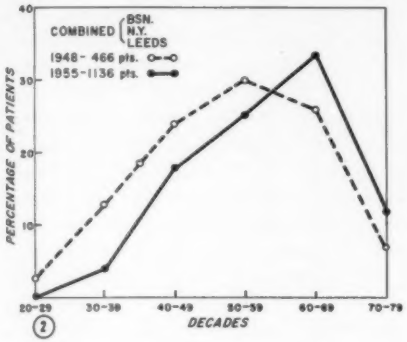
Date of Birth	Date of Onset								
	Before 1920	1920/24	25/29	30/34	35/39	40/44	45/49	50/54	55/60
1865/69				5				1	
1870/74				3	3	4	5	2	
1875/79		2		1	8	4	15	13	1
1880/84	1		3	6	9	8	36	33	1
1885/89		2	5	7	6	15	41	62	
1890/94		3	4	7	10	13	40	62	1
1895/99		1	3	8	9	11	31	50	
1900/04		2	4	6	10	10	36	28	
1905/09		3	8	6	9	8	22	23	
1910/14	1	6	5	4	3	7	8	14	
1915/19				3	5	5	13	5	1
1920/24				1	1	2	2	1	
1925/29							1		
1930/34									
Totals:	2	19	32	57	73	87	250	294	4
Per cent Decades:	2½%		11%		19½%		67%		

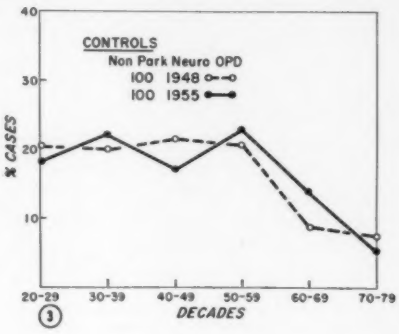
relationship between the concentration of cases in the ten years, 1945 to 1954, and the duration of the influenza epidemic, 1917 to 1926. Table 3 shows these data plotted out in decades.

Distribution curves for the ages of patients during 1955 were made for the three groups of patients as follows: 400 (Boston), 547 (New York), and 200 (Leeds), and for the three groups of patients in 1948. These three groups are essentially similar to each other, showing peaks between ages 50 and 60 in 1948 and between ages 60 and 70 in 1955. There is a definite shift of the younger patients from 1948 and 1955 in all three groups so that none was under 30 years old in the 1955 group. The peak is the same in all three curves, and in the older group there is an increase in all three groups between ages 70 and 80 from the 1948 values.

All of these distribution curves are arranged on a percentage basis of the total number of patients involved. For example, the peak of the Boston group in 1948 involves 35 per cent of the total patients, the New York group 29 per cent, and the Leeds group 37 per cent. In 1955 the peak of the three groups between 60 and 69 years was the Boston group with 36 per cent, New York group 34 per cent, and Leeds 28 per cent. When these three groups are added and the total percentage obtained and plotted in decades as shown in figure 2, it will be seen that there is a total shift of the distribution curve to the right of about ten years between the two decades. The addition of the two other groups of patients confirms the age distribution shift as originally reported in Boston.

It is quite obvious that no conclusions can be drawn from this population shift unless it is specific for parkinsonism and not found in other conditions. A series of non-parkinson neurologic outpatient





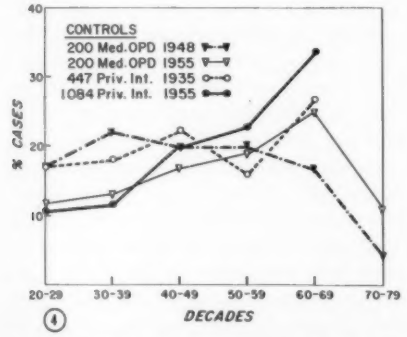


FIG. 2. Shift in age distribution between 1948 and 1955 in the combined groups from Boston, New York, and Leeds, England.
FIG. 3. Age distribution curves of neurologic outpatient cases at the Massachusetts General Hospital in the years 1948 and 1955.
FIG. 4. Age distribution curves of outpatient medical cases at the Massachusetts General Hospital in the years 1948 and 1955, and also the private medical cases in 1935 and 1955 of Dr. Allen S. Johnson.

cases for 1948 and 1955 were plotted in the same way on a percentage basis. This series has to be enlarged. No such distribution curve was encountered and the two curves crossed each other three times in the course of the six decades studied. This is shown in figure 3. Another group of controls was plotted in the same way using 200 consecutive records of the medical outpatient clinic for 1948 and 1955, which did not include parkinsonism. This group shows a slightly similar age distribution shift, so that in 1948 there were more younger patients and less older ones, and vice versa for 1955. It must be pointed out, however, that the shape of the curves is very different from the parkinsonism shift and the material consists of a mixture of many kinds of patients. It is obvious that there is an increase of survival of the degenerative diseases at the present time, so that hypertension and cardiovascular disease are more common in survival groups and there is a disappearance of the acute infectious cases which are now treated with penicillin and other antibiotics.

In this same figure 3, a second group of medical patients was plotted from Johnson's data[2] concerning the age distribution of medical patients from 1935 to 1955, and, excluding those under 20 years of age, the percentage in decades resembles the medical outpatient cases somewhat. There is a greater reversal in 1955 of the number of younger patients seen and an increase in 1955 roughly cor-

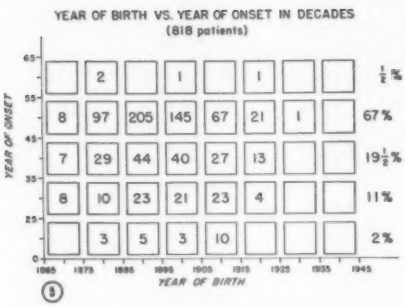


FIG. 5. Relationship of date of birth arranged in decades and plotted against the date of onset of the symptoms in decades in 818 patients.

responding to the older patients. The same mixture of cases as noted in the outpatient group occurred.

DISCUSSION

It is obvious that no definite conclusions can be drawn from this material as it is presented. In the first place it will require a lapse of approximately three to five years to ascertain whether the peak in the influenza onset versus the date of onset chart still has such an abrupt fall after 34 years. Secondly, it would be highly advantageous to obtain an age distribution curve of the shift from 1948 to 1955 in a fourth group of parkinsonism cases from another part of the world, namely, south of the equator. This is being arranged by Dr. David Fairman of Buenos Aires, Argentina. Fairman's 200 cases have just become available. There is no data for 1948 since there was no clinic then. The 1955 age distribution curve shows the same peak and form as our curve for that year. The plot of year of onset with date of birth peaks, as ours does, in 1950 and falls off to only three in 1955. We would also like to enlarge greatly the study of the non-neurologic outpatient cases to see if a more satisfactory comparative distribution curve could be plotted before drawing any comparative conclusions. It might be well to obtain distribution curves for the two years 1948 and 1955 for specific degenerative medical disease, such as arthritis, hypertension, or cerebral vascular accidents. These data will be correlated as they become available to us.

The concentration of patients in the decade 1945 to 1954, commented on previously, is best shown in figure 4, where they are grouped into decades and the highest concentration on the fourth line of such decades is easily seen. It is to be noted that 205 of the 818 patients actually had onset of parkinsonism between 1945 and 1954, and were born between 1885 and 1895. This represents 25 per cent of the total group of patients in a total of 40 decades.

Strangely enough, in spite of the fact that there have been reports in the literature of parkinsonism in children[3] and this disease has been familiar to neurologists ever since Parkinson's original description[4] in 1817, none of the patients in our group of 1,147 was born after 1926.

To summarize the agreement in the age shift curves as mentioned in the text, there was no difference in the form of the curves in the three groups from Boston, New York, or Leeds, nor was there any difference in private or clinic patients.

Although there is some clinical difference between so-called postencephalitic parkinsonism and parkinsonism beginning in the setting of arteriosclerotic disease, there are no good criteria for such separation. The absence of oculogyric crises in the elderly group is cited as a difference. There are some data that

these crises tend to disappear as one survives into the older group. Furthermore patients who are exposed to the infectious process allegedly responsible for a majority of these cases, if they were under 20 years of age when they had influenza, would have their infection at a time when the nervous system was growing and where there was clearly no evidence of degeneration from aging. They might well have a slightly different pathologic picture. There is a tendency for this kind of virus infection to be more severe in the younger age group, particularly children, and to be better tolerated in the more maturely formed brains. In the actual pathology of the disease there is no really good pathologic difference between these groups except that the postencephalitic type seems to involve a wider area than the so-called idiopathic type. This involvement of the cortex in severe encephalitic cases with mental impairment is quite different from the more localized process in the elderly where only lesions in the substantia nigra and reticular brain structures are found.

Concerning the type of initial symptom encountered by patients with parkinsonism, this information was obtained originally from all our patients and, during the year in which this paper was being prepared, was checked whenever possible in subsequent interviews with the patient. In the case of the other two series, information was obtained from the patients or from their records by the collaborating physician in the group. Preliminary analysis of our material shows that 80 per cent of all patients with parkinsonism begin their disease either with tremor (50 per cent) or rigidity (30 per cent). The remaining 20 per cent are divided between 10 per cent impairment of motor activity (category 3), 8 per cent general diffuse symptoms (category 4), and only 2 per cent are in the miscellaneous range. Since the tremor is so conspicuous and easy to identify by both the patient and the examining physician, we believe that the date of onset of this disease as related to tremor and rigidity is fairly accurate. The fourth category, general and diffuse symptoms, which accounts for only 8 per cent of the total series, may very well antedate the tremor and rigidity in a number of patients as this particular type of symptom is thoroughly investigated.[5]

Many patients whose date of onset was determined by the beginning of the tremor might have shown fatigue and non-medical symptoms for many years previous, such as slowness in letting go of a tool used in the patient's trade or occupation, or a tendency for the hand or arm to get into awkward positions of which the patient was unaware. This suggests that the long period of latency between the alleged influenza attack and the appearance of tremor and rigidity may be quite false and that the milder nonclinical symptoms may have been present for several years.

A spot check of the history of influenza during 1917 to 1926 or encephalitis where we have definite information that the patient and his relatives were specifically questioned, there was a positive history in 75 or 58 per cent of 129 cases. The usual reported incidence is considerably less than this because the question often is not asked. The average incidence is around 50 per cent and one would expect with a very careful history in every patient that it might be more than the 58 per cent encountered

in this check. Further investigation of this point will be necessary in the future.

CONCLUSIONS

1. Three groups of patients with parkinsonism totaling 1,147 were surveyed as to their age distribution in 1948 and 1955. Patients came from three cities: Boston, New York, and Leeds, England.

2. A definite shift in the peak of the distribution curve from 50 to 60 years in 1948 to 60 to 70 years in 1955 was found in all three groups of patients.

3. Sixty-seven per cent of 818 patients began their disease, regardless of age, between the years 1945 and 1954. Seventy-one per cent of the same number fell within 25 to 34 years after their (true, 58 per cent; assumed, 42 per cent) influenza infection. These two 10-year periods suggest a relationship because the epidemic ran ten years, from 1917 to 1926.

4. A control series of nonparkinson neurologic patients shows no such distribution shift, but medical patients, both outpatient and in the private practice of an internist where the ratio of infectious to degenerative diseases has obviously changed, show different kinds of shift but along the same lines.

5. These data might point to a possible common etiology between two-thirds of parkinsonism patients and the influenza epidemic in 1917 to 1926, and, therefore, a drop in the number of patients with this disease might be expected during the next ten years.

The authors are greatly indebted to Dr. Mandel Cohen of the Massachusetts General Hospital neurology department, who went over this data and made a number of constructive suggestions about plotting it in graph form and in comparing it to non-parkinson medical material.

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■ The blood vessels, like muscles of animal life, may have spasms, as well as they may be paralyzed. In certain injuries to the nervous centres there are spasms produced in the blood vessels of many parts of one-half of the body, at the same time that there are paralysis and dilatation of those of the other half of the body. A section of a lateral half of the spinal cord near the medulla oblongata produces this curious effect; on the side injured, the blood vessels of the extremities are paralyzed; while on the opposite side they are spasmodically contracted. Very often the spasm persists for days, and after temporary relaxations it alternately reappears and disappears again.

The spasm of blood vessels may be so great that circulation is almost entirely suspended; the temperature of the limbs (especially that of the toes) falls quicker than after death, and it is soon at nearly the same degree as that of the atmosphere. In one case, in a dog, we have seen the temperature of the toes on the left side, after the section of the right half of the cord in the cervical region, falling from 26 Centigrade (78.8 Fhr.). In the toes, on the right side, the temperature had increased extremely and reached 36 Cent. (96.8 Fahr.).

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Brain Swelling of Unknown Cause

A. L. Sahs, M.D. and R. J. Joynt, M.D.

PATIENTS exhibiting evidence of increased intracranial pressure and suspected of harboring brain tumors continue to present a challenge to the neurologist and neurosurgeon. In 1939 Sahs and Hyndman,[1] reporting upon experiences with five cases in which this syndrome presented, postulated that they were dealing not with serous meningitis, hydrocephalus, or encephalitis but with brain edema of unknown cause. Since then 17 additional cases have been encountered. These have been studied more thoroughly than was feasible in the earlier cases. In the present communication microscopic observations and long-term follow-up studies are emphasized.

These cases have been variously designated pseudotumor, serous meningitis, serous arachnoiditis, chronic arachnoiditis, otitic hydrocephalus, toxic hydrocephalus, and so on. Before the advent of ventriculography a great deal of confusion attended attempts to identify the condition, and present day understanding of the pathogenesis of the disorder has been delimited by the fact that for the most part we are dealing with a nonfatal process.

Quincke[2] appears to have been one of the first to recognize the condition. He reported ten cases of "serous meningitis" and emphasized that the signs of increased intracranial pressure were associated with clear spinal fluid. A review of his series indicates that the application of modern diagnostic technics probably would have excluded several of his cases. Warrington[3] reviewed the literature up to 1914 and expressed the opinion that the most common associated condition is otitis media. He called attention to the possibility that toxins circulating in the blood stream are responsible for the intracranial disorder. A critical review of his cases suggests that he was dealing with a rather heterogeneous group of conditions. Passot[4] suggested that the disorder might be considered a hypertensive state and mentioned that the condition is more common among children and adolescents than adults. He described the clinical picture as characterized by progressive headache, drowsiness, papilledema, and clear spinal fluid under increased pressure and having normal constituents. Passot believed that the condition was produced by an excess of fluid in the

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subarachnoid space. Claude[5] reviewed the entire subject and considered encephalitis, trauma, and infection to be the likely etiologic factors. He was the first among recent authors to emphasize the value of air studies in diagnosing the disorder.

Symonds[6] correctly noted the absence of localizing signs in "otitic hydrocephalus" and asserted that the clinical picture was ascribable to increased intracranial pressure alone. On critical examination it appears warranted to exclude two of Symonds' three cases from further consideration, the first on the basis of its being an instance of hydrocephalus following meningitis and the second on the ground that the spinal fluid was grossly cloudy. Later, Symonds[7] indicated that the mechanism of increased intracranial pressure associated with thrombosis within the dural sinuses is by no means certain. He felt that it might be due to obstruction of the arachnoid villi or to cerebral edema from venous engorgement or both.

The report of Davidoff and Dyke[8] stands as the first accurate description of "serous meningitis" in modern literature. Air studies were performed in all of their 15 patients, of whom 11 were females and four males. Most of their patients were relatively young. The history of otitis media was present in four cases; in two others there was a history of infection elsewhere in the body some time before the onset of the intracranial complication. Davidoff and Dyke emphasized that a "wet brain," the subarachnoid spaces of which were distended with fluid, was a common finding at operation. They stated that, when the arachnoid membrane was broken, a jet rose ten or more centimeters. The cerebrospinal fluid flowed off in large amounts and the intracranial pressure, which in some instances was quite high, was perceptibly diminished.

McAlpine[9] objected to the term "serous meningitis" and introduced that of "toxic hydrocephalus." He suggested that toxins affected the secretion of the choroid plexus and concluded that the hydrocephalus was of an external type. The adjective "toxic" as used by McAlpine refers to toxins derived from distant sources of infection, such as those of the middle ear, nasopharynx, and other portions of the body. This author employed air studies in two of his five cases.

The comprehensive report of Dandy,[10] entitled "Intracranial Pressure without Brain Tumor," appeared in 1937. Twenty-two cases were reviewed in detail, all of which had been subjected to air studies. The author asserted that he did not know the exact etiology of the condition but conjectured that the intracranial hypertension was dependent upon the intracranial fluid content (blood and/or spinal fluid). He contended that the very rapid changes in the size of decompressions could not be explained readily in other terms and held that the variabilities in fluid content must occur in the brain itself rather than in the meningeal spaces, because 1) the protruding brain at the time of operation is only partially, and at times scarcely at all, relieved by evacuating the fluid from the subarachnoid spaces over the temporal lobe, and 2) the ventricular system is always small, usually appreciably smaller than normal. Dandy reasoned that if the amount of subarachnoid fluid were increased, the ventricular system would ultimately participate and, therefore, be correspondingly dilated from the backlog. He asserted that fluid

is never in the subdural spaces in these cases and contended that the only other place it could form in excess so as to produce intracranial hypertension would be in the substance of the brain; he suggested that the only other possible explanation of the increased pressure was by variation in the intracranial vascular bed, probably by vasomotor control.

Zuidema and Cohen[11] followed up 12 of the original 22 cases reported by Dandy. Ten were alive and well, one was later found to have an intracranial aneurysm, and one was reported elsewhere as having multiple sclerosis. Zuidema and Cohen reported 39 additional cases with follow-up studies of 26. There were 21 survivors. These authors indicated that many, if not most, such cases constitute unrecognized instances of dural sinus thrombosis, whether or not the complication is preceded by a respiratory or middle ear infection. In 1939 Ford and Murphy[12] enumerated the multiple causes of increased intracranial pressure and listed brain swelling of unknown origin apart from thrombosis of the dural sinuses.

Ray and Dunbar[13] and Ray, Dunbar, and Dotter[14] utilized angiographic visualization of the superior longitudinal sinus in an effort to demonstrate venous thrombosis as the possible cause of this disorder. Attempts along this line had been made previously by Frenckner[15] and by Gardner.[16] Gardner indicated that thrombosis does not necessarily involve the sagittal sinus in order to produce increased intracranial pressure. He considered that if one of the lateral sinuses constituted the chief emissary for the intracranial circulation, its thrombosis would suffice to produce increased intracranial pressure. Ray and Dunbar[17] called attention to the observation that obstruction of the sagittal sinus alone, or in conjunction with a transverse sinus, or obstruction of both transverse sinuses with sparing of the sagittal sinus could produce an increase in intracranial pressure. Such was regarded as a purely mechanical result of obstruction of the intracranial venous system, having little or nothing to do with overproduction of spinal fluid or reduction in its absorption.

Wagener[18] in 1954 reviewed the literature and concluded that most cases of true "pseudotumor cerebri" with normal ventriculograms and chemically and cytologically normal cerebrospinal fluid represented instances of cerebral edema, and thus constituted a group separate from that of dural sinus thrombosis. Dunn, Baker, and Wagener[19] indicated that cases of "pseudotumor cerebri" represented examples of swelling of the brain or edema resulting from water-electrolyte imbalance, and that the disturbance could be initiated by toxic, inflammatory, hormonal, allergic, or other factors. McCullagh[20] had previously reported detailed chemical studies on a 24 year old woman with the clinical picture of "pseudotumor cerebri" and severe menstrual edema.

Foley[21] has divided this general group of cases into 1) otitic cases, in which thrombosis of the major lateral sinus is the probable cause of the raised pressure; 2) a larger group in which there is no history of infection or injury, consisting almost exclusively of women, with a peak incidence in the fourth decade; and 3) a smaller group in which the condition follows an infection or mild head injury, the sexes being afflicted equally and the age at onset tending to be lower than in the second group. According to Foley, there is little evidence that throm-

bosis of venous sinuses is responsible for the second or third groups. Rapid visual failure is not encountered in the otitic cases. It is relatively common, however, in the other groups.

Martin[22] reported five cases in which there were papilledema and other signs of increased intracranial pressure following slight head injuries. Four of these cases had localizing neurologic signs at some period in their illness. In each case there was an interval between the injury and the advent of signs of increased intracranial pressure. Martin attributed the increased pressure to obstruction of the superior sagittal or major lateral sinus, due either to thrombosis spreading from emissary veins or, more likely, to injury of the dura in the sinus wall.

Berg and co-workers,[23] in studying 238 cases of increased intracranial pressure without localizing signs, found that in 27, or 11 per cent, the final diagnosis was "serous meningitis." They found lateralized mass lesions much more frequently than "serous meningitis" in patients who presented themselves with increased intracranial pressure alone.

Our present study began in 1939 and adds 17 cases to the group originally reported by Sahs and Hyndman[1] (table 1). The criteria for the diagnosis have been outlined by many authors and consist essentially of bilateral papilledema, normal or small ventricles, normal cerebrospinal fluid (except for increased pressure), and no localizing neurologic signs.

In none of these patients was there evidence of ear disease or mastoiditis at the time of admission to the hospital. Two patients gave a history of head injury within two months of admission, the severity of injury being originally considered slight. Cortical biopsies were obtained in ten instances. All 17 patients have been followed by letter or direct examination. Sixteen have been followed for more than two years, and nine have been contacted ten years or more after their first visit to the University Hospital.

ILLUSTRATIVE CASES

Case 5. M. K. (table 1). A white woman, aged 27, was admitted to the hospital on September 28, 1939. She complained of bitemporal headaches which had been present for one year and blurring of vision of two months' duration. She had had recurrent attacks of bronchitis for a year prior to the onset of her headaches, but there was no history of ear infection.

One year before admission she began to have headaches in both temples. These were more frequent in the evenings and were aggravated by lying down. They were only partially relieved by analgesics. The more severe headaches were attended by nausea. Two months before the patient entered the hospital she noticed failing vision in the left eye. Shortly thereafter vision in the right eye was similarly impaired. She complained of blunting of mental acuity and occasionally she experienced diplopia. There was no history of alteration of her menstrual function. She had not experienced recent change in weight and there was no syncope or convulsions. The strength of her extremities was excellent and coordination was well preserved.

At the time of admission she weighed 213 pounds. She was alert and cooperative. Her temperature was 98.8° F. and the pulse rate was 72 per minute. She presented the appearance of an individual with severe visual impairment. Visual acuity was 6/60 in the right eye and in the left, 6/360, corrected. The right nerve head showed 3 diopters elevation and appeared to be twice its normal diameter. The retinal veins were distended and several subretinal hemorrhages were noted along the course of the inferior retinal vessels. The left disk showed approximately the same amount of elevation. Irregular field defects were demonstrated in both eyes in the form of peripheral constriction, more severe on the left than on

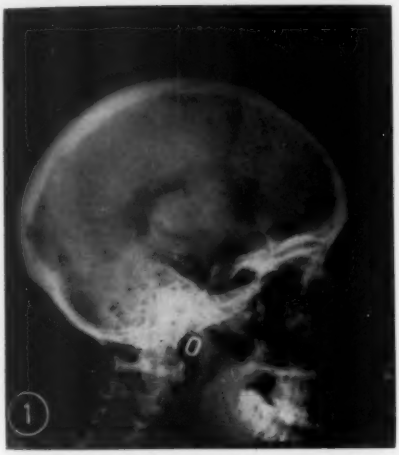

FIG. 1. *(Case 5)* Lateral ventriculogram showing a filling defect in the left lateral ventricle. This defect was proved at operation to have been produced by a fresh blood clot.

the right. The blind spots were greatly enlarged. The pupils reacted well to light and in accommodation. The extraocular rotations were normal and there was no evidence of squint. Hearing was within normal limits and the facial movements were symmetric. There was no nuchal rigidity. Examination of the chest and abdomen was not remarkable. The blood pressure was 130/80. Motor power in the extremities, coordination, reflexes, and sensory status were normal.

The specific gravity of the urine was 1.017. There was no albumin, sugar, or blood in the urine. The hemoglobin value was 14 gm., the erythrocyte count 5.1 million, and the leukocyte count 7,850 per cu.mm. Serologic reactions of the blood were negative for syphilis. The spinal fluid, clear and colorless, disclosed an initial pressure of 285 mm. as measured in the lateral horizontal position. The fluid contained four lymphocytes per cu.mm. and the Pandy reaction for globulin was negative. The Meyers reaction for blood was likewise negative. The total protein value of the spinal fluid was 29 mg. per 100 cc. and the chloride value 765 mg. per 100 cc. Serologic tests on the spinal fluid were negative for syphilis. The electroencephalogram was reported as follows: "16 leads, entirely normal, both monopolar and bipolar." Roentgenograms of the chest and skull were normal.

On October 6, 1939 a ventriculogram was performed. Satisfactory filling was accomplished after the usual posteriorly-placed trephines were made. Ventriculographic studies showed a filling defect within the left lateral ventricle (figure 1). However, the ventricular system was of normal size and exhibited no displacement.

Because of the unusual ventriculographic picture, exploration was accomplished through a left frontal flap. No note was made concerning the appearance of the meninges. The cortex of the brain appeared normal. A core of tissue was removed from the left frontal lobe, exposing the anterior horn of the lateral ventricle. A fresh clot the size of a hazel nut was removed from the anterior horn and a somewhat smaller one from the third ventricle through the foramen of Monro.

The blood clots were immediately fixed in a 10 per cent solution of formalin. In addition, the core of brain tissue, which measured 2.5 cm. in diameter, was placed in the fixative. The postoperative course was uneventful except for a slight elevation of temperature for several days. Subsequent lumbar punctures within a period of several weeks following operation showed an initial pressure averaging 200 mm. of water. The patient was discharged from the hospital on the twentieth postoperative day without any significant change in the appearance of her fundi. The decompression site was bulging moderately.

She returned to the hospital on January 11, 1940. At that time vision in the right eye was 6/6, and in the left 6/180. Secondary optic atrophy was present. The blind spots were still enlarged and there were irregular defects in the nasal portions of each visual field. The initial pressure of the spinal fluid at this time was 260 mm. of water.

The patient was examined several times during the next few years. She continued to complain of variable amounts of headache and backache, but she was able to work almost full time. Secondary optic atrophy was by now very much in evidence. The decompression site gradually became sunken. A letter from the patient dated October 5, 1946 indicated that she was quite "nervous" and still suffered from occasional headaches. Vision in the left eye was reported poor, but the patient asserted

that she was capable of full-time work as a housewife. A letter dated August 29, 1955 reported that she was "feeling fine" except for occasional headaches. Her vision was still poor. She was working full time as a housewife. There were no convulsions.

Microscopic examination of the blood clots indicated that they were composed of red blood cells without evidence of organization. The brain tissue was studied with a variety of stains which are reported as follows:

Myelin sheath stain (Pal-Weigert) showed no evidence of myelin degeneration. Of particular interest, however, was the spongy appearance of the brain. The perivascular spaces were swollen. A striking amount of intracellular or pericellular edema, or both, was scattered diffusely throughout the entire white matter, giving the white matter a "cheesy" appearance. Stains for fatty products of degeneration (Sudan IV) showed no unusual accumulations of free fat either in the ganglion cells or in the white matter of the brain.

Hematoxylin and eosin stains revealed tremendous swelling of the cellular elements and "lakes" of intercellular edema (figure 2). The oligodendrocytes seemed to be particularly affected (figure 3). There was an appreciable amount of distention of the vessels and dilatation of the perivascular spaces.

Nissl's stain showed a normal-appearing arachnoid and considerable distention of the intracerebral vessels. There was an unusual amount of swelling of the nuclei of the ganglion cells and an uneven staining of the Nissl substance. The latter was crowded to the periphery of the cells. Careful search revealed no lesions that could be interpreted as inflammatory in type.

The Penfield modification of the Hortega silver carbonate impregnation for oligodendrocytes showed striking changes in these cells, the alterations being in the form of severe swelling of the cell bodies (figure 4). The astrocytes, as studied by the Cajal gold sublimate impregnation, were not increased in number but exhibited hypertrophy (figure 5).

Comment: This patient presented the clinical features of brain swelling as previously outlined. The spinal fluid pressure was increased and there was bilateral papilledema. There were no localizing signs. She is alive and reasonably well 16 years after her illness began. One finding that requires account is the unusual disclosure of blood clots in the ventricular system. The accidental production of injury to the glomus of the choroid plexus is a rare occurrence as an incident to ventriculography, but attention has been drawn to this circumstance by Dyke, Elsberg, and Davidoff.[24] Since microscopic observation in this instance revealed fresh clot without evidence of organization, it seems reasonable to suppose that the blood clots were produced during ventriculography. Support is lent to this view by the fact that the lumbar puncture previous to operation showed no evidence of blood or xanthochromia in the cerebrospinal fluid.

Case 17. G. B. (table 1). A 17 year old male was admitted to the hospital on June 19, 1950. He complained of blurred vision and photophobia of two and one-half months' and headaches of two weeks' duration.

Two years prior to the onset of the present illness the patient had had a grand mal seizure. Similar attacks had recurred at irregular intervals. An aura of numbness of the right hand heralded the third seizure. The patient was otherwise well until April 1950 when he developed intermittent blurring of vision and photophobia. At this time he also had a right otitis media which was painful for two days. This was treated with penicillin and rapidly subsided. Later the patient experienced generalized and bifrontal headaches without nausea or vomiting. No personality change or alteration in consciousness was noted at any time.

At the time of admission he was alert and did not appear ill. His temperature was 98.4° F. and the pulse rate 72 per minute. There were bilateral papilledema with a disk elevation of 3.5 diopters, venous distention, and no hemorrhages. There were no focal neurologic signs. The general physical examination, including examination of the ears, was normal. The blood pressure was 124/70. The specific gravity of the urine was 1.005. No albumin, sugar, blood, or casts were revealed in the urine. The hemo-

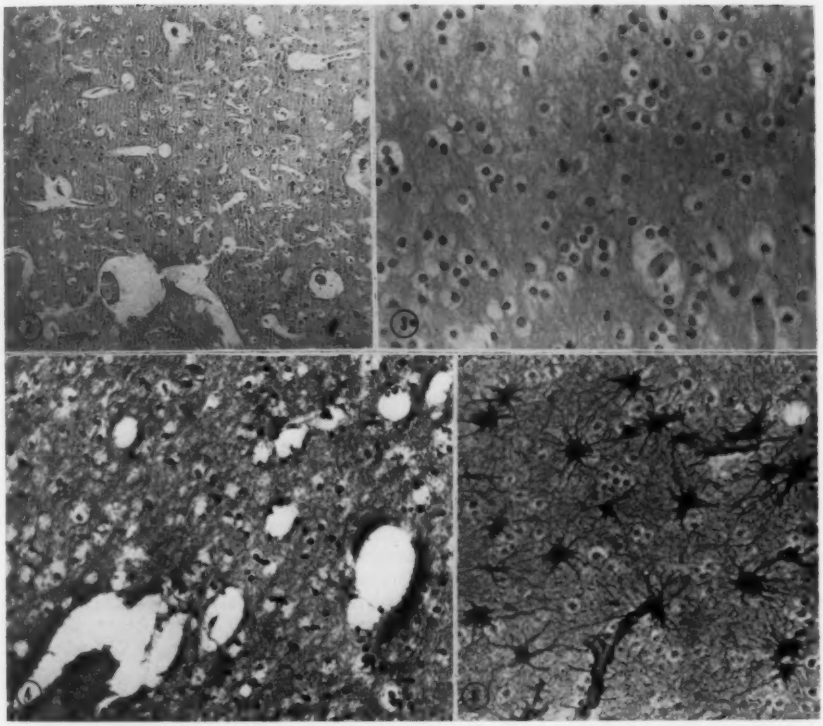

FIG. 2. *(Case 5)* Photomicrograph of gray matter in frontal cortex showing cerebral edema. Hematoxylin and eosin stain.

FIG. 3. Photomicrograph of white matter in frontal lobe. There is extreme swelling of the oligodendroglial cells and conspicuous interstitial edema. Hematoxylin and eosin stain.

FIG. 4. Photomicrograph of white matter. Penfield modification of the Hortega silver carbonate impregnation.

FIG. 5. Photomicrograph of white matter showing hypertrophy of the macrocytes. Cajal gold sublimate impregnation.

globin value was 13.5 gm. and the erythrocyte count 4.57 million per cu.mm. The leukocyte count was 5,250 per cu.mm. with a normal differential count.

On June 21, 1950 a ventriculogram was performed. The dura was tense and the brain bulged into each parietal burr hole. The ventricles were cannulated with difficulty. Roentgen examination revealed incomplete filling, but the ventricles appeared very narrow and the third ventricle consisted of but a narrow slit. A left frontotemporoparietal craniotomy decompression was accomplished. The dura appeared normal but was extremely tight. The cortex appeared swollen but otherwise grossly normal. The cortical arteries and veins appeared normal. It was not possible to visualize the superior sagittal sinus. A biopsy was taken from the precentral gyrus.

Postoperatively the papilledema subsided slightly by the seventh day, but the brain remained tense. Because of this, a sagittal sinus venogram was performed on July 5, 1950, and demonstrated patency of the sagittal sinus, torcular, lateral sinuses, and upper jugular bulb (figure 6). The patient was discharged four

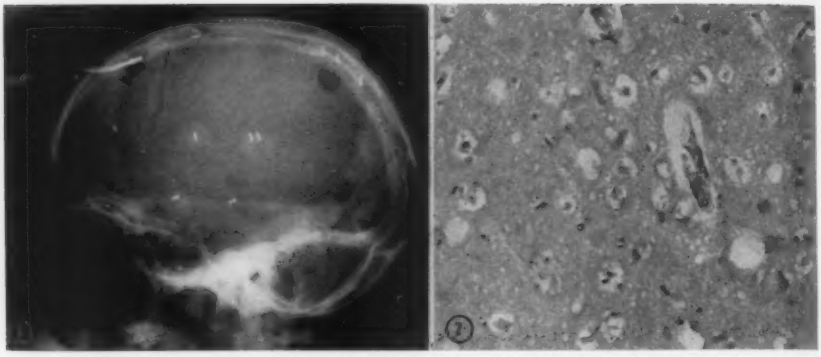

FIG. 6. *(Case 17)* Venogram showing patency of the superior sagittal and lateral sinuses.
FIG. 7. Photomicrograph demonstrating cerebral edema. Hematoxylin and eosin stain.

days later on 100 mg. of Dilantin three times daily.

He was examined Juiy 18, 1950, by which time he had improved greatly. The optic disks were flat and the neurologic examination was normal. The decompression site still bulged slightly. On December 27, 1950 an attempt was made to cover the decompression site with a tantalum plate. The brain was exposed and rebiopsied. During anesthesia the cortex bulged inordinately and for this reason it was decided to abandon the attempt. Following this procedure, the patient had several right-sided jacksonian convulsions which were controlled with Dilantin. The biopsy showed no evidence of neoplasm.

The patient was reexamined several times. There was little regression of the bulging at the decompression site. The parents and the patient noted that the area of the decompression varied in its protuberance at different times throughout the day and during physical strain or exertion. It was regularly prominent after a night's sleep.

An electroencephalogram performed in May 1953 revealed diffuse 1½ to 3½ per sec. and 4 to 7 per sec. waves over the left hemisphere.

The defect was covered with a tantalum plate on March 22, 1954. The patient continues to do well, although he has an occasional seizure despite continuous use of Dilantin and phenobarbital.

The microscopic appearance of the tissue removed at the original biopsy showed no evidence of myelin degeneration, inflammatory disease of the brain, or stainable free fat. Brain swelling, both intra- and extracellular in type, could be seen in all sections. The swelling was rather patchy and involved the gray as well as the white matter. The oligodendroglia in particular were swollen. The perivascular spaces were greatly widened (figure 7). No vascular lesions were seen to account for the edema.

Comment: The histologic findings in this case were similar to those of case 5. The clinical picture was complicated by seizures which from their onset did not appear to be related to the episode of cerebral edema. At the height of the illness, patency of the superior sagittal and lateral sinus was demonstrated by venography.

Biopsies from the brains of the other eight cases showed a similar pattern to that described in cases 5 and 17 and therefore need not be reviewed in detail here. No inflammatory foci were found and the location of the lesions did not suggest an obvious perivascular arrangement. The swelling in every instance was both extra- and intracellular.

For control purposes, six normal cortical biopsies were chosen at random. These had been obtained in an attempt

to establish the diagnosis of certain psychotic conditions. The sections showed fraying of the brain substance at the edges, with some evidence of acute edema of the ganglion cells. However, even in the small biopsies, the deepest portions were relatively intact and none presented the severe interstitial and intracellular edema observed in the brain swelling cases.

Finally, for purposes of comparison, an attempt was made to determine whether any characteristic alterations might be identified in the brain biopsy of a patient with proved thrombosis of the superior sagittal sinus.

B. J., a 58 year old telephone operator, was admitted to the hospital on January 27, 1956, complaining of headaches and blurred vision of three months' duration.

In 1948 the patient had a left radical mastectomy for carcinoma of the breast. Her progress was satisfactory until April 1955 when a nodule was found in the left axilla. This lesion was biopsied and the patient was informed that there was no evidence of malignancy. Following this procedure, a persistent edema of the left arm developed. The patient's neurologic symptoms started three months prior to admission, with frequent supraorbital headaches which lasted four to six hours and abated spontaneously. Later she noticed that upon arising a "full feeling" developed in the head and she experienced transient unsteadiness. Two months prior to admission vision began to fail and the patient developed diplopia. These symptoms continued until her admission. She had had no recent weight loss.

Upon arrival at the hospital she was alert and did not appear desperately ill. Her temperature was 98.6° F., pulse rate 88 per minute, respiratory rate 28 per minute, and blood pressure 148/96. The optic disks revealed 3 to 4 diopters elevation and central hemorrhages were evident. Neurologic examination was otherwise within normal limits. A small, nonmobile, tender nodule was felt in the midoccipital region of the scalp.

The specific gravity of the urine was 1.015 and no albumin, sugar, blood, or casts were present. The hemoglobin was 10.5 gm. and the leukocyte count 9,700 per cu. mm. Skull films showed an osteolytic lesion in the left occipital region. Chest films were normal. Radioactive iodinated serum albumin studies revealed the greatest uptake in the left parieto-occipital region. An electroencephalogram revealed some minimal focal activity (6 to 7 per sec. theta and 3 to 4 per sec. delta waves) over the left posterior quadrant.

FIG. 8. *(B. J.)* Oblique venogram showing residual air in the ventricular system and obstruction of dye proximal to the torcular Herophili with collateral venous channels evident.

On February 6, 1956 ventriculography was performed. The brain did not appear swollen. Ventricular filling was incomplete, but no evidence of a space-taking lesion was found. A sagittal sinus phlebogram was performed and showed a complete block of the radiopaque material immediately proximal to the region of the torcular Herophili (figure 8). On February 13, 1956 a lumbar puncture disclosed an initial pressure of 300 mm. of fluid and a final pressure of 210 mm. following removal of 6 cc. of clear fluid. The total protein value was 73 mg. per 100 cc.

On February 16, 1956 a biopsy specimen was removed from the lesion in the occipital bone and another was taken from the right parietal cortex. The bone lesion was diagnosed as ana-

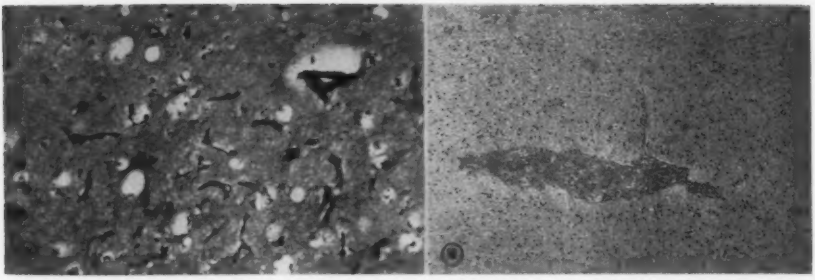

FIG. 9. *(B. J.)* Photomicrograph of white matter in parietal lobe with intracellular and perivascular edema evident. Penfield stain.

FIG. 10. Photomicrograph of white matter showing distention of vessel, thickening of vessel wall, occasional macrophages, and perivascular lightening. Hematoxylin and eosin stain.

plastic malignant neoplasm, consistent with metastatic scirrhous carcinoma of the breast.

Microscopic sections of the cortical biopsy showed considerable diffuse swelling of the brain involving both gray and white matter. Of the various elements, the oligodendroglia and the perivascular spaces were involved particularly (figure 9). Similar swelling was also seen in the ganglion cells. A few vascular changes in the nature of distention of the vessels were discernible. Here and there zones of perivascular lightening were noted, and in some areas the vessels walls were thicker than normal and contained a few macrophages (figure 10).

Comment: This case illustrates that a superior sagittal sinus thrombosis sufficient to give radiologic evidence of phlebographic block can exist without producing localizing signs or alteration in consciousness. The microscopic appearance is not unlike that found in the previous cases of brain swelling of unknown origin, except for the perivascular lightening and changes in the vessel walls. This may be a significant finding, but inasmuch as one case only is available a generalization is not warranted.

The clinical histories, physical and laboratory findings, operative procedures, and ultimate outcome of the 17 cases are outlined in table 1.* The general characteristics of these 17 cases are similar to the 60 previously collected from the literature and summarized by Foley.[21] A striking feature is that ten of the 11 cases which had their onset after the age of puberty occurred in women; the peak incidence was in the third decade. A similar preponderance of women is also found in the large series of Dandy,[10] Zuidema and Cohen,[11] and Foley.[21] Another unusual occurrence is obesity; the average weight of nine of the ten women with recorded weight was 182 pounds. Although only three patients were excessively heavy, all females were overweight for height and age. Foley[21] observed obesity in 20 of 28 females in his second category, that is, those without a history of antecedent infection. Among the 14 adult females in Dandy's series, seven were considered overweight or obese and two as "large." The association of brain swelling with pregnancy and menstrual disturbances commented on by Foley[21] was not evident in our cases.

Among the eight cases of our series

*Six additional patients were originally diagnosed tentatively as brain swelling of unknown etiology. One of these refused ventriculography; the other five were later diagnosed as basilar meningitis, infectious polyneuritis, encephalitis, probable chicken-pox encephalitis, and hematohygroma.

TABLE 1

SUMMARY OF CLINICAL FINDINGS, OPERATIVE PROCEDURES, AND OUTCOME IN 17 CASES OF BRAIN SWELLING OF UNKNOWN CAUSE

					Symptoms							*Findings*									*Laboratory Findings*					*Surgery*				*Ultimate Results*				
Patient	Age on admission	Follow-up years	Duration symptoms (mo.)	Recent infections (2 mo.)	Recent head injury (2 mo.)	Headaches	Vomiting	Dizziness	Tinnitus	Visual failure	Diplopia	Convulsions	Height	Weight	Blood pressure	Temperature	Papilledema diopters	Retinal hemorrhages	Sixth nerve palsy	Other signs	Previous pregnancies	Serology	CSF pressure	Cells	Protein	Skull films	EEG	Ventriculograms	Decompression	Biopsy	State of dura	Life	Vision	Papilledema	Convulsions	Recurrences
AB	28	10	9			+	+	+			+	+		200	14/8	99	5				N	330	2	20	N		N	+	+	B	+	I	S		
HB	24	14	3	+		+							63	145	11/7	100	2	+			2	N	250	4	35	N	N	N	+	+	B	+		N		
CT	22	11	2		+	+				+	+		65	177	14/8	99	4	+				N	320	3	38	N		N	+	+	B	+	I	S		
MB	18	12	1	+		+				+				185	12/8	98	6	+				N				N		N	+	+	T	+	I	N		+
MK	27	16	12			+	+			+	+		62	213	13/8	99	3					N	285	8	29	N	N	A	+	+	B	+	I			
JK	21	10	1			+	+						63	229	15/7	99	+	+				N	220	2	38	N		N				+	I	N		
IT	32	13	6	+		+	+						64	138	11/7	99	2				3	N	360	3	24	N		N	+	+	B	+	I	S		
ME	23	1	1			+		+	+	+			65	200	13/8	99	5				1	N				N		N	+		B	+	I	N		
JR	23	3	3			+	+									99	1	+			2	N	270	4	29	N		N			T	+				
EM	44	7	2			+				+				154	12/8	99	2	+				N				N	N	N			N	+	I	S		
JS	7	2	1			+	+				+		45	43	10/8	99	+		+			N	280	8	6	N		N			T	+	I			
JM	4	16	1	+		+	+			+					12/8	99	4	+	+			N	475	4	N	A		N	+	+	B	+	I	N		
RB	8	10	3	+	+	+				+	+		52	64	12/8	100	6		+			N	250	2	38	A		N	+	+	T	+	I	N		
MF	12	6	1			+		+						105	12/6	99	3					N				A		N		+	B	+		N		
DS	12	3	1	+			+	+			+					100	2	+					240	0	20	N		N			N	+	I	N		
JD	11	7	6	+		+				+	+		58	78	11/7	99	3					N	165	0	24	N		N			N	+	I	N		
GB	17	6	3	+		+				+		+			12/7	99	5					N					A	N	+	+	B	+		N	+	

+, present or performed N, negative or normal A, abnormal B, bulging T, tense
, subsiding at time of last examination I, improved

*Cases 1 to 11, inclusive, plus case 16, were females. Total—12
Cases 12 to 15, inclusive, plus case 17, were males. Total— 5

that had had an infection within two months of the onset of symptoms, three occurred in the adult group and five in children under 12. Those in the adult group consisted of tuberculosis, pharyngitis, and pyelitis, respectively. The younger group had "flu," "draining ears," ear infection, and "swollen joints." In none of the cases other than the tuberculous patient was there any sign of active infection when the patient was admitted. Three patients in this group gave a history of a recent ear infection, but at the time of admission there were no obvious signs of activity. The additional features of this series need not be mentioned as they are quite similar to others reported in the literature in regard to history, signs and symptoms, laboratory findings, and ultimate outcome.

Study of the underlying disease process in this condition has been seriously impeded by the lack of pathologic specimens. Ventriculography has clarified the issue of hydrocephalus: it is now generally accepted that the ventricles are either normal or of smaller than normal size. The presence of an increased amount of cerebrospinal fluid in the subarachnoid space is still mentioned as a possible explanation for this condition, but in only one reported case (Dandy,[10] case 4) was evacuation of all available cerebrospinal fluid accomplished incidental to pneumoencephalography and in this instance only 75 cc. was obtained. Sahs and Hyndman[1] suggested that it would be impossible for excess fluid to be present as a result of decreased absorption of the cerebrospinal fluid without ventricular dilata-

tion, and that any excess fluid noted might be part of the general edematous process.

Some of Dandy's[10] patients reported a rapid change in the tension of the decompression site, a circumstance that led him to conclude that the manifest changes in the intracranial pressure could be effected only by alterations in the cerebrovascular bed and thus in the volume of blood. This postulate, of course, does not explain the chronic increase in intracranial pressure that may exist for months or years. It must be said, however, that Dandy did not offer the vascular theory as being the only process at work. By exclusion, the only portion of the intracranial contents remaining is the brain substance itself, and our biopsy material supports the contention that this is a major factor in the production of brain swelling.

Evidence obtained from biopsy material must be accepted with some reservation because of the inevitable distortion that comes with handling such tissue and because the amount of tissue is necessarily small. The block of tissue obtained from case 5 was sufficiently large to be relatively intact, at least in its deepest portions. We were impressed with the profound swelling present in the material obtained from these cases. Since evidence is accumulating that these are not instances of hydrocephalus or meningitis, there seems to be very little doubt that these are examples of intrinsic brain swelling affecting gray and white matter and involving the intracellular and interstitial areas. We did not differentiate between brain swelling and brain edema but believe, as do Greenfield[25] and Perret and Kernohan,[26] that the fundamental process is similar and that they differ only in degree.

The etiology of the brain edema remains unsettled. As noted above, the role of thrombosis of the intracranial dural sinuses has been advanced by Symonds[7] and Ray and Dunbar.[13] The question arises whether all cases of "pseudotumor" fall into this category. Wagener,[18] Dunn, Baker, and Wagener,[19] and Foley[21] are of the opinion that other explanations must be entertained to account for a significant proportion of the cases in this group. We have shown that a somewhat similar pathologic picture can be observed in cases with and without radiologic evidence of dural sinus thrombosis. Comprehension of the phenomenon of brain swelling (cerebral edema) has proved to be a most elusive subject, and investigators should not consider the matter closed by the demonstration of dural sinus thrombosis in some of the cases previously considered as "pseudotumor cerebri" or "otitic hydrocephalus." We would like to emphasize the importance of continued observation of the cases clinically, careful pathologic studies when available, and the utilization of newer radiologic and biochemical technics, as well as blood flow studies. The heightened occurrence of this disorder in obese females raises certain questions which fall logically into the metabolic and hormonal fields.

Finally, it must be admitted that "brain swelling of unknown cause" can be mimicked by a number of conditions, and that the clinical impression must be established by careful examination of the spinal fluid, ventriculograms, possibly dural sinograms, and reexamination before one can be certain that a correct diagnosis has been reached. Once the condition has been identified, most patients will recover spontaneously. The

physician needs to be concerned with the condition of the vision and to gauge the indications for continued conservative management or surgical decompression by progress examinations of the visual acuity and optic disks.

SUMMARY AND CONCLUSIONS

1. Long-term follow-up studies are recorded in 17 cases of brain swelling.

2. Biopsy material from ten of these cases has been studied. Microscopic sections show intracellular and extracellular edema.

3. In one of these 17 cases of brain swelling, patent superior longitudinal and lateral sinuses were demonstrated.

4. In one instance of proved dural sinus thrombosis, the swelling resembled that seen in the 17 cases listed above, except for vascular alterations.

5. It is suggested that continued studies be made of cases of brain swelling, with particular reference to pathologic examination, utilization of newer radiologic and biochemical technics, as well as blood flow studies.

6. The heightened occurrence in obese females raises the question of metabolic and hormonal disturbances.

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Differential Diagnosis in Patients with Co-existing Neurologic and Neurosurgical Disorders

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THE GOAL of the neurologist is to determine the presence, nature, and location of a lesion involving the nervous system. The aim is to localize the pathology in one spot, one area which fulfills all the physiologic manifestations. Thus, the brainstem with its cranial nerves and converging pathways is the happy hunting ground of the scholarly bent. Some diseases, however, have multiple foci, for example, syphilis, disseminated sclerosis, viral encephalomyelitis, and so on. The neurologist tries to find one disease which will account for all the physiologic defects. This single-target discipline is of particular importance to the neurosurgeon, since he perforce could not treat one site while the pathologic process proceeded at another. Such thinking, however, has its pitfalls. The autopsy table often reveals that the patient has more than one disease. Certain nosologic clinical entities may mask the signs of another. For example, a multiple-focus medical, neurologic disease may cover the signs of a single-focus surgically identifiable one, or a peripheral neuron impairment may hide an upper neuron lesion. The symptoms of a long established illness may lull the examiner into a sense of security, while a new disease with simulating symptoms is evolving elsewhere.

The following examples of co-existing neurologic disease, medical and surgical, will serve to illustrate these points.

Case 1. A 52 year old woman gave a history of having fallen from a ladder 17 years ago. Since then she had experienced low back pain, with radiation down the lateral aspect of the left thigh to the knee. Coughing and straining increased the pain. Other than absent abdominal reflexes, the neurologic findings were confined to the left lower extremity. Here there was an absent ankle jerk and a decrease in sensitivity to pin-prick and cotton touch over L_{4-5} and S_1. The left calf was atrophied. Spinal fluid protein was 41 mg. per cent, and the myelogram showed a defect at L_4. At surgery a disk was removed between L_4 and L_5 and the patient did well postoperatively.

Two months later, however, she returned complaining of "paralysis" around the waist, pain in the right foot, and the feeling of a "hole" in her right hip. She was evaluated as a complainer and sent home on heat, massage, and exercise.

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Six months later she entered another clinic complaining of weakness and numbness in both legs and a mild pain in her right hip. Following the disk operation she had also noted a new numbness in the right foot and leg, as well as a new weakness in that leg. During the next four months she developed numbness over the abdomen, as well as urinary frequency.

Now there was a sensory level to pin-prick to T_{10}. Vibration was absent to the right and left knees. Both limbs were generally weak. The deep reflexes were hyperactive with bilateral Babinski signs and abdominal reflexes were absent. Spinal fluid showed a prompt rise on jugular compression but a slow fall. The spinal fluid protein was 45 mg. per cent, and the myelogram revealed a filling defect at L_3 and a total block at T_{10}. A meningioma was subsequently removed at T_9.

Case 2. A 33 year old woman developed acute loss of vision four years before in her left eye, which was diagnosed as retrobulbar neuritis. This cleared in part over the following few months. A year later she noted paresthesias of her left leg which lasted for several months, then disappeared completely. Eighteen months before, she developed pain in the dorsal scapular region which radiated around the right to the sternum. This was made worse by coughing. Eight months earlier her legs became "funny." This increased to weakness on the right, with numbness up to the waist. She stated that she had multiple sclerosis, described it as a terrible disease, but was euphoric and casual as she spoke. On questioning she admitted some loss of control of bladder and bowel.

Examination revealed spastic paraplegia in extension. There were bilateral Babinski signs with flexor synergias on plantar stimulation. Ankle jerks were brisk and there was a beginning right Hoffmann reaction. Abdominal reflexes were absent and there was no Beevor's sign. Vibration sense was absent to T_6, pin-prick to T_{3-4}, and cotton touch to T_3. Sympathetic reflexes were absent below T_5. Sensation was normal over the upper trunk, head, and neck. The extraocular muscle movements were normal and there was no nystagmus. The pupils were equal; however, the right pupil reacted better to light than the left. Optic nerve heads were flat, but the left had a yellowish-white color.

Spinal fluid pressure was 50 mm. and rose slowly on jugular compression with a slow fall. Total protein was 132 mg. per cent. Thoracic spine roentgenograms were normal, but the myelogram showed a block at the T_3 vertebra. At operation a meningioma was found on the left anterolateral surface of the cord opposite the T_3 interspace. She did well postoperatively with early signs of sensory and motor return.

Two and one-half years later she was readmitted because, for the preceding few months, paralysis had begun to increase again. The wound was reopened. There was no recurrence of the tumor, no significant adhesions, or other mechanical defects. She has continued to run downhill progressively, as in a degenerative disease, with spasms and sphincter involvement.

Case 3. A 44 year old housewife entered the hospital complaining of "stiffness" from the waist to the toes on the right side, with an inability to feel heat and cold on the left from the foot to the hip. This had been going on for nine months. She described the muscles of the right chest as "sore." During the previous year she had noted difficulty in starting the urinary stream and felt a loss of force in emptying her bladder.

The general physical examination was normal except for blood pressure of 160/100. Both lower limbs were ataxic and weak, with coarse tremors on the heel-to-knee test. The deep reflexes on the right were greater and there was right ankle clonus. Bilateral Babinski signs were present with right Oppenheim and Chaddock signs. There was a suggestive right Hoffmann's sign. The abdominal reflexes were not elicited. The right face was slightly flattened, the right palpebral fissure widened, and the right face not as expressive as the left. Vibration sense was absent on the right to the costal margin, with a loss of joint sense in the right foot. Pin-prick produced a hyperpathic response in the right lower limb. Heat and cold were absent on the left to T_{12}, L_1.

Roentgenograms of the thoracic and lumbar spine were normal. The spinal fluid dynamics were normal with a protein of 43 mg. per cent. Two lesions were postulated, a modified Brown-Sequard, chiefly right, above T_9, probably coming from without, inward, and another in the brainstem or subcortical white matter in the left cerebrum. A question of multiple sclerosis was raised and the patient was given histamine empirically. She was watched closely for new signs. Within two weeks the sensory level had risen to T_6 and was not bilateral. The spinal

fluid examination now revealed no response to the Queckenstedt maneuver and the protein was 55 mg. per cent. A myelogram showed a block between T_1 and T_5, and at surgery a meningioma was removed at T_4 on the right. The patient recovered all her functions rapidly and walked out of the hospital 20 days after surgery.

One year later, however, she complained of pain at the base of her skull, lapsed into coma, and died six hours later. Autopsy revealed a fresh basilar subarachnoid hemorrhage. Free blood was present in both lateral ventricles. Small areas of softening were seen in both frontal lobes, but on the left a 4.5 by 3.5 by 3.2 cm. cavity communicated by a small tract with the left lateral ventricle. This area of softening was old.

Case 4. A 60 year old corporation president was brought into the hospital by his daughter who felt that her father was becoming incompetent. The family had been told that he had a very severe form of arteriosclerotic brain disease and that he could not be expected to assume much responsibility. The patient was confused and occasionally fell asleep during the examination. He admitted headache and complained of strange odors about him. He also mentioned a previous episode of dragging of his left foot.

An examination was difficult because of the patient's lethargy. All movements of the left arm were poor and he perseverated with this limb. The deep reflexes were slightly greater on the left and a fragmentary Rossolimo was noted but no other pathologic reflexes. Sensory responses were equivocal because the patient fell asleep during the testing. The left face (lower two-thirds) was weak, but the tongue protruded in the midline and there was no aphasia, apraxia, or astereognosis. A well-developed arcus senilis was present and the patient looked older than his 60 years. The optic nerve heads were flat and the vessels sclerotic, but the right disk showed a suspicious elevation of the superior margin. This lifted more in the next few days and the vessels in this area became engorged. The skull film showed a 5 mm. pineal shift to the left, and the electroencephalogram revealed a slow-wave focus in the right fronto-anterior temporal region. Operation exposed a right frontal lobe astrocytoma in an arteriosclerotic brain.

Case 5. A 55 year old salesman gave a long-standing history of menianopic migraine, usually right-sided, but entered the hospital because he felt his headaches had "changed." They were now consistently right-sided and, in addition, he experienced flashes of red and blue light in both eyes which had no special form or character. He mentioned becoming easily upset, at times even confused, and he also complained of blurred vision and a sensation of being "top-heavy."

General physical examination was negative. The neurologic examiner was impressed by the fact that the patient was lying in bed with his left arm almost crushed under him. The left lower limb was also in a grotesque position, externally rotated. The deep reflexes were slightly greater on the left, with a beginning Babinski response on that side. The left abdominal reflexes were absent, the right present. There was a homonymous hemianopic field defect. Left body image was lost and stimuli on the left, called to his attention, were referred to the right side. Left finger agnosia was demonstrable. His left face (lower two-thirds) was weaker than the right. The optic nerve heads were flat, but there was a suggestive fullness of the vessels on the right. White count was 10,750. A skull film revealed a pineal shift to the left, and the electroencephalogram showed a focus in the right parietal lobe. At surgery a huge parieto-occipital lobe abscess was evacuated. Now four years later the patient remains symptom-free.

Case 6. A 57 year old dairy executive, a known luetic, entered the hospital because of a recent onset of weakness on his right side and difficulty in speech. Earlier he had noted numbness of his fingers on the right and found that he could no longer shift the gears of his automobile. He was given a course of penicillin, only to become worse. His right leg began to drag and he could no longer hold objects in his right hand. He went to bed clear of mind one night and awakened shakey and confused. His appetite had been poor for three weeks and he had lost ten pounds.

Examination revealed a lethargic man who was old for his years. Blood pressure was 170/70. He was restless, confused, and could not sit up unassisted. He perseverated in his movements. Physical examination was normal except for a left heart enlargement, a water-hammer pulse, and systolic and diastolic murmurs at the heart base. He was incontinent.

Only crude movements could be performed on the right. Right ankle clonus was present. Deep reflexes were brisk and varied from side to side with no predominance. Bilateral Babinski and Hoffmann signs were present. Right abdominal and cremasteric reflexes were absent, the left present. Cotton-touch and pinprick sensations were normal. The right face (lower two-thirds) was weaker than the left and the tongue protruded to the right. Both pupils reacted poorly to light and accommodation. The optic nerve heads were flat. The patient could not recognize objects placed in his right hand and he lost awareness of his left arm. He gradually developed paraphasia.

Two weeks earlier spinal fluid studies elsewhere had shown a positive Kahn and Wassermann, with a midzone Lange gold curve and a protein of 16 mg. per cent. At this hospital the initial cerebral spinal fluid pressure was 400 mm., with a drop to 210 after 5 cc. of fluid were removed. The protein was now 83 mg. per cent, with eight cells and a beginning first zone gold curve. A space-occupying lesion was now more suspected. Spinal fluid Kahn and Wassermann were negative; however, the blood Wassermann was 3 plus. White count was 17,750, with a normal differential.

The electorencephalogram showed an abnormally slow, diffuse record with the greatest abnormality in the left temporoparietal region. Skull films were normal. A chest film was done, seeking for a primary lesion, and showed an area of infiltration in the right middle lobe. Bronchoscopic smear was negative for tumor.

The patient died 18 days after admission. Autopsy revealed a tiny, marble-sized tumor in the right middle lobe, which was proved histologically to be a bronchiogenic carcinoma. The aorta showed atherosclerosis plus typical luetic changes. The brain had a large metastasis in each parietal lobe.

In summary, we have presented six illustrative cases. The first was a patient with a proved herniated lumbar disk, with later development of new motor and sensory findings leading to the surgical removal of a mid-thoracic level meningioma. The second was a woman with multiple sclerosis who subsequently revealed a meningioma at T_2. The next was a middle-aged woman with cord as well as cerebral symptoms, leading to the initial working diagnosis of multiple sclerosis, but within two weeks she was shown to have a thoracic level meningioma. One year later she died of cerebral hemorrhage and showed an old area of cerebral softening on a vascular basis. The fourth was a 60 year old man with a history of cerebral arteriosclerosis who developed confusion, headache, and was found to have a frontal lobe astrocytoma. The next was a middle-aged man with a history of hemianopic migraine who developed a "different kind of headache" with visual hallucinations and who at surgery demonstrated a large parieto-occipital lobe abscess. The last case, a known luetic with hypertension and arteriosclerosis, presented findings of weight loss, bilateral parietal lobe defect, and increased intracranial pressure. Autopsy confirmed the presence of cerebral metastatic lesions.

The conclusions to be drawn from this study are simple. Most diseases have a fairly typical history or typical exceptions. The more one knows of a disease, the more skillfully one employs the ancillary devices of the laboratory. Nothing in the latter can ever be substituted for a careful history review and for repeated neurologic examinations, both pre- and postoperatively. All the facts must be weighed and assembled, and even then, the mind must be kept open for the possibility of further or new pathology. The conscientious neurologist, utilizing his broad knowledge and experience, is in the most strategic position to render the mature judgments necessary to give the neurologic patient his best care.

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Maurice Victor, M.D. and C. G. Tedeschi, M.D.*

CASE PRESENTATION

A 22 year old white male printer was admitted to the Los Angeles Veterans Administration Hospital on December 29, 1954. In June 1954 the patient had noted occasional blurring of vision, disturbed balance, diplopia, and excessive tearing of the right eye. In mid-December he developed a left middle ear infection which was treated with penicillin. The ear was irrigated, causing intense pain and making the patient faint. That evening he complained of left earache and headache; the ear drained pus and blood for three days thereafter. Four days later, on December 15, he awoke in the morning with numbness of the right side of the face and stiffness, weakness, and incoordination of the left arm and leg; he had difficulty in pronouncing words and swallowing. These symptoms gradually became more severe. There was no vomiting, tinnitus, vertigo, or convulsions. Snce 1953 he had had two bouts of acute otitis media and was said to have had a perforated ear drum. Since childhood he had noticed uncontrollable clonic movements of both feet on marked plantar flexion. He was left-handed. Other past history was not contributory.

Physical examination. The patient was a tall asthetic young white male, with a temperature of 97° F., pulse 60 and regular, and blood pressure 108/80. Both tympanic membranes were intact, the left slightly retracted. The neck was supple. No nodes were palpable. Heart and lungs were normal. Abdomen was scaphoid and soft. Liver and spleen were not felt. He was oriented in all spheres and memory was intact. Speech was quite dysarthric and rather explosive. Visual fields and acuity were grossly normal. Optic disks were normal. Extraocular movements were intact and pupils were equal and reacted to light. There was hypesthesia and hypalgesia over the first and second divisions of the right trigeminal nerve and left facial weakness with slight weakness of frontalis and orbicularis oculi muscles. Corneal reflexes were intact. He had moderate dysphagia, and gag reflexes were absent. There was partial paralysis of the right vocal cord. The Romberg sign was positive, the patient falling to the left, and both left extremities were quite ataxic. There was a moderate spastic left hemiparesis. All deep tendon reflexes were hyperactive, more so on the left, and there were bilateral Babinski signs and poorly sustained bilateral ankle clonus. Abdominal reflexes were equivocal. Sensation was intact except for the right trigeminal nerve.

Laboratory findings. Hemoglobin 15.8 gm., hematocrit 45 per cent, white cell count 7,600, neutrophils 53, lymphocytes 36, monocytes 5, eosinophils 6 per cent. Urinalysis: specific gravity 1.028, albumni 1+, sugar negative, sediment negative. Serology negative. Blood urea nitrogen 10 mg. per cent, fasting blood sugar 90 mg. per cent. Lumbar puncture: Initial pressure 220 mm., clear fluid, Pandy negative, protein 33 mg. per cent, sugar 54 mg. per cent, chloride 119 mEq., one white cell, two red cells, serology negative.

Chest, mastoid, and skull films were negative except for some prominence of digital markings. The electroencephalogram was negative.

From the Veterans Administration Hospital, Boston, Massachusetts.

Hospital course. Initially the patient's speech improved considerably and the paralysis of the right vocal cord disappeared. However, about one month after admission he rapidly became dysarthric and was unable to speak above a whisper. Several new signs and symptoms appeared: diplopia on looking to the right with weakness of the right lateral rectus muscle; altered perception of pain and touch on the right side of the tongue; bilateral diminution of corneal reflexes; marked weakness of the masseter and pterygoid muscles so that he was unable to chew food; facial weakness on the right as well as the left, and bilateral weakness of tongue muscles with moderate atrophy of the tongue on the left. Left hemiparesis became more severe, and there was also some involvement of the right arm and leg. During the sixth hospital week he had a sudden onset of fever of 102° F., cough and dyspnea, rales in the chest, and a patch of pneumonic infiltration in the left lung, all of which cleared fairly promptly with penicillin. Repeat skull films and electroencephalogram were negative. A repeat lumbar puncture showed an opening pressure of 250 mm. water, six lymphocytes, and 42 mg. per cent.

On March 2, 1955 he was transferred to the Boston Veterans Administration Hospital. At this time he could extend and flex the fingers of the right hand weakly. These were the only voluntary movements he could make. There was marked increase in tone in all extremities, more marked on the left. Corneal reflexes were absent. He could swallow only with extreme effort and was unable to speak. There was ptosis of the right upper eyelid and bilateral facial weakness was marked. Sensory examination was somewhat difficult because of poor communication, but there was a suggestion of a sensory level at C3. Abdominal reflexes were absent. There was severe generalized wasting but no evidence of muscular atrophy. Otherwise findings were the same as those in Los Angeles. Hemoglobin was 13.7 gm., white cell count 10,600, neutrophils 77 per cent, and lymphocytes 23 per cent. Urinalysis showed 1+ albumin and 10 to 25 white cells per high-power field. Lumbar puncture revealed an initial pressure of 450 mm., 450 fresh red cells, 2 lymphocytes, Pandy negative, protein 14 mg. per cent, serology negative. Skull films were negative. An electroencephalogram showed an abnormal record characterized wholly by low voltage slow activity of five to seven per second throughout, with some rare slower waves in the occipital leads.

Again initially there was some subjective improvement. Diplopia disappeared and he was able to move the toes on both feet slightly. Thereafter his course was progressively downhill. He became incontinent of urine and developed urinary infection due to *A. ærogenes* and *Pseudomonas æruginosa*, which was refractory to treatment. Inability to expel respiratory secretions required frequent endotracheal suction, and he had repeated bouts of pneumonia for which he received penicillin. He was fed with difficulty via nasogastric tube and parenteral fluid. In late July he gradually became comatose, with Cheyne-Stokes respirations, and he expired on August 3, 1955.

CLINICAL DISCUSSION

DR. MAURICE VICTOR:* To facilitate the discussion, it might be useful to separate the patient's symptoms into two groups. One group concerns the clonic movements of the feet. We are told only that this disorder dated from childhood and it is not amplified any further. It may have been an entirely separate disorder with no bearing on the final illness, but this will be a matter for future speculation. The second group of symptoms are those which began in June 1954. These are obviously the important ones to consider, for they marked the onset of a progressive illness which proved lethal 14 months later.

Anatomically, the latter symptoms point to the posterior fossa—more specifically to the cerebellum and lower brainstem structures. The evidence for this is clear enough. The earliest symptoms were disturbed balance and diplopia; later there was facial numbness, incoordination of the left arm and leg, dysphagia, and dysarthria. The description of the speech disturbance as "explosive" marks it as cerebellar in nature. What is described as ataxia of the left arm and leg was probably also cerebellar, since it was not due to sensory or motor loss; sensation was said to be normal and weakness was only moderate at the time the ataxia was noted.

Weakness of the jaw muscles and diminution of the corneal reflexes, paralysis of the right vocal cord, and weakness of the tongue implicate the fifth, tenth, and twelfth

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cranial nerves, respectively. Furthermore, the fact that vocal cord paralysis was unilateral and the tongue weakness was accompanied by focal atrophy indicates that the disorder of function was the result of direct involvement of the nuclei of these nerves or their peripheral extensions and was not the result of a pseudobulbar palsy, that is, an interruption of the corticobulbar tracts at an upper brainstem or cerebral level.

The first problem to be settled is whether the pathologic process was intrinsic in the brainstem, or whether it arose outside the brainstem and cerebellum and produced its effects by compression or distortion of these structures.

My inclination is to regard this process as intrinsic. The most cogent reason for this view is the relatively early and profound affection of pyramidal tract function. At a relatively early stage in the illness (five months before death), the patient was practically incapable of voluntary movement of any sort. With lesions outside of the brainstem, as with an acoustic neurinoma for example, pyramidal tract function may be disturbed; such involvement, however, is usually partial in degree and less prominent than the cranial nerve disturbance. A bothersome point in this regard is the apparent sparing of sensory tracts. If one postulates an intrinsic pathologic process successively affecting cranial nerve nuclei, pyramidal tract, and cerebellar connection, it would be inconsistent for the sensory tracts to remain undamaged. In the note from the Los Angeles Veterans Administration Hospital, spinothalamic and medial lemniscus functions were reportedly intact. Later it was stated that the sensory examination was made difficult because of trouble in communication and that there was a suggestion of a sensory level at C3. The sensory tracts may well have been involved, and the lack of more specific information concerning the sensory defect should not deter us from placing the lesion within the brain structures themselves.

I shall assume, therefore, that we are dealing with an intrinsic disease of the pons and medulla, affecting the tegmentum and the base bilaterally and affecting also the cerebellar peduncles. If this concept is correct, one can immediately exclude tumors of the cerebellopontine angle, such as acoustic neurinoma, meningioma, glioma, ependymoma, and true cholesteatoma, as well as other lesions of the angle, such as adhesive arachnoiditis following otitis media. It would also be difficult to conceive of such lesions running their entire course without affecting the eighth nerve or elevating the spinal fluid protein.

Neoplasm is the only intrinsic lesion that merits serious consideration, although vascular, infectious, and demyelinative lesions should be mentioned for completeness. An angioma of the pons produces its effects by intermittent episodes of bleeding; neither of these features was present here – the disease progressed in a nonapoplectic manner and at no time did the spinal fluid disclose any blood. The possibility of an abscess of the cerebellum with extension into the pons should be mentioned in view of the chronic otitis media. For such a disease to run its entire course without fever and without elevating the cells or protein in the spinal fluid would be most unusual. A relatively acute instance of multiple sclerosis limited to the brainstem is a distinct diagnostic possibility. The fact that "initially his speech improved considerably and the paralysis of the right vocal cord disappeared" could be construed as evidence of remission. The fact that all the signs could be explained by a disease process in one locus in the nervous system should make us reluctant to accept a clinical diagnosis of multiple sclerosis. The normality of the spinal fluid in terms of cells, total protein, and globulin is also very much against the diagnosis of multiple sclerosis, for one or other of these constituents are abnormal in the majority of cases. Nor could the gradually increasing spinal fluid pressure be explained by demyelinative

disease; it would be entirely in keeping with an expanding lesion. Neoplasm, then, is the diagnosis which most effectively satisfies the entire clinical picture. The course of the illness was all in all inexorably progressive. The improvement that occurred in the course of the illness was clear enough, but of a limited nature. It is difficult to explain such an event in a brainstem glioma, but in practice it does occur and is entirely compatible with the diagnosis of tumor.

The one remaining problem in defining the pathology concerns the bilateral clonus which the patient reportedly had since early childhood. Was this a neurologic disturbance quite unrelated to his final illness? Or did the patient suffer a neurologic disorder since early childhood, which remained quiescent for many years and finally reasserted itself at age 22?

If the two disorders are indeed related, the diagnostic possibilities are extremely limited. One would have to consider platybasia, Arnold-Chiari malformation, syringomyelia, and dermoid cyst. Most of these can be logically eliminated in short order. The patient had none of the clinical or radiologic features of platybasia. The Arnold-Chiari malformation may indeed be characterized by hydrocephalus, cerebellar symptoms, cranial nerve palsies, and long tract signs. The hydrocephalus and lower cranial nerve signs tend to be more prominent in the Arnold-Chiari malformation, whereas in our case there was a prominent affection of the upper cranial nerves and pyramidal tracts. Neoplastic growth may occasionally complicate syringomyelia, but there was no segmental motor, sensory, and reflex loss which are so characteristic of that disease. Dermoid cysts in the posterior fossa are usually tucked between the cerebellum and the pons, or between the cerebellum and the medulla. The major objection to this diagnosis is the one that applies to extrinsic lesions in general.

I would return then to a diagnosis of intrinsic neoplasm of the pons and medulla. The type of tumor which would occur in this locality, at this age, and which would progress at this tempo would most likely be a glioma, more specifically, a glioblastoma multiforme.

DR. VICTOR'S DIAGNOSIS: Glioblastoma multiforme of the brainstem (pons and medulla).

ANATOMIC DIAGNOSIS: Astrocytoma, grade III to IV, of the pons.

PATHOLOGIC DISCUSSION

DR. C. G. TEDESCHI:* Postmortem examination confirmed the presence of a tumor in the pons. In the upper pons the growth was characterized by a poorly demarcated, soft, grey-pink nodule which extended from the right side to the midline into the tegmentum. In the lower portion of the pons the tumor was more diffuse. It occupied almost entirely the basis pontis and had grown into the right cerebral peduncle to about the level of the midthalamus and the posterior limb of the internal capsule. The areas involved by the neoplasm were soft and hemorrhagic in places, with an orange-brown discoloration which suggested extensive tissue necrosis.

Recently aspirated blood was found in the air passages and this most probably was the event that precipitated the death of the patient. Attention has been drawn repeatedly to the occurrence of acute mucosal erosions in the lower portion of the esophagus, stomach, and duodenum, and less frequently in the jejunum in connection with brain injury, particularly hypothalamic lesions.[1–5] In this case, also, poorly demarcated brownish erosions were found in the esophageal mucosa and a small amount of digested blood, about 100 cc., was present in the gastric cavity. These erosions were most likely the source of the bleeding that led to aspiration of blood in the air passages. Various stages of lobular pneumonia were also shown in different portions of both lungs, recent in some areas, organizing in other areas. Although no definite food material could be identified, the occa-

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sional presence of foamy or coarsely vacuolated lipid-containing macrophages suggested that aspiration of food particles must have occurred on several occasions.

As correctly suggested by Dr. Victor, the pontine tumor on histologic examination proved to be a rapidly-growing astrocytoma. Prominent feature of the growth was marked cellular pleomorphism, which is interpreted as indicating many gradations of anaplasia. As shown in figure 1, large cell bodies with hyperchromic nuclei and heavy, shortened processes irregularly alternate with more anaplastic cells with large bizarre-shaped nuclei, often several nuclei, and scarcely recognizable rudimentary processes which no longer can be identified as astrocytic elements. In view of the pronounced cellular anaplasia, one would have expected to find marked mitotic activity; instead mitoses were hard to recognize, possibly because many of the nuclei were pyknotic.

Abundant vascularity was another prominent feature of the growth (figure 2). The majority of the blood channels were thin-walled with large lumens. Proliferation of adventitial and endothelial cells, which is so frequently found in cerebral tumors similar to the one under consideration, was not present in our case. However, the imperfect structure and fragility of these newly-formed blood vessels was reflected by the frequent extravasation of red cells.

Invasion by tumor cells into adjacent structures, which grossly had appeared well-preserved, had taken place; therefore, the border between tumor and normal tissue was indistinct and even the relatively normal-appearing areas showed increased cellularity.

The problem arises at this point as to the label best befitting the characteristics of the tumor. No other category of neoplasms has longer resisted attempts of orderly classification than those of the nervous system. In 1926 Bailey and Cushing[6] proposed a classification of gliomas which has proved a great stimulus to further studies in this field. It was based on the assumed resemblance of the various cells in gliomas to embryonic glia cells during development. According to this concept, each tumor had a distinctive predominant cell type which mirrored a certain stage in the embryonic development of the astroblast. Tumors characterized by the presence of immature cells, which were reminiscent of cells of the astrocytic series in early phases of development, they named "astroblastomas;" tumors composed of better-differentiated cells, which closely resembled the mature astrocyte at the end-stage of its development, were termed "astrocytomas." However, soon it became apparent that, whereas the astrocytoma had found a secure position in this scheme of classification, other less-differentiated tumors scarcely fit within the architectural pattern of the life history of the astroblast. This was found to be particularly true for a category of tumors, well exemplified by our own, characterized by pronounced cellular pleomorphism and by the presence of multinucleated giant cells, none of which can be identified with any of the cell types met in the embryonal development of astrocytic elements. On the assumption that this particular type of tumor reflected some of the cytologic patterns of the embryonal spongioblast, Globus and Strauss[7] proposed to name it "spongioblastoma multiforme." But others did not recognize this resemblance and the tumor was arbitrarily renamed "glioblastoma multiforme."

A more recent approach to the problem by Kernohan and his associates,[8] based on the concept that the pleomorphism evidenced by these neoplasms reflects various degrees of cellular dedifferentiation of the astrocyte rather than arrests in different phases of its embryonal development, has resulted in a favorably received proposal of new classification. By analyzing these tumors from the standpoint of anaplasia or dedifferentiation, as indicated by pleomorphism, hyperchromatism, and mitotic activity, these authors arrived at the conclusion that four grades of malignancy could be conveniently established and for each of

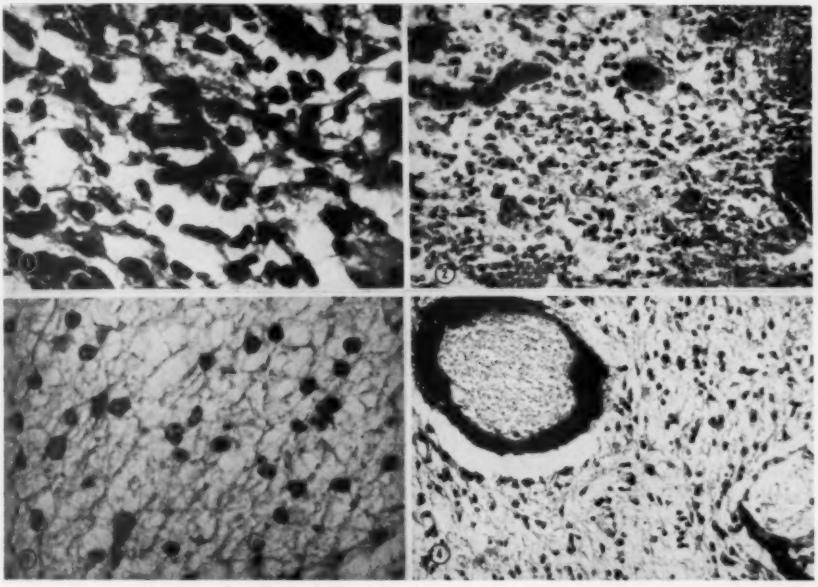

FIG. 1. Marked cellular pleomorphism and hyperchromatic, bizarre-shaped nuclei interpreted as indicating various degrees of dedifferentiation of astrocytic elements in the pontine tumor. Diagnosis: Astrocytoma grades 3 to 4.

FIG. 2. Numerous thin-walled blood channels and extravasated red cells within the tumor. Notice the absence of adventitial and endothelial cell proliferation, a change that frequently occurs in astrocytomas of high grade.

FIG. 3. Well-differentiated neoplastic astrocytes with abundant fibrillary development within the otherwise poorly-differentiated malignancy. This finding is interpreted as suggesting the origin of the highly anaplastic pontine tumor from a pre-existing astrocytoma of lower grade.

FIG. 4. Heavy deposition of lime salts in the wall of blood channels in the area of less cellular dedifferentiation.

these four grades they set up the basic criteria. Tumors characterized by relatively normal-appearing astrocytes with no anaplasia were fitted into the category "grade 1." Early anaplastic transformation of a small number of cells, in the absence of mitotic figures, were felt to characterize the "grade 2" category. In the category "grade 3" they allocated growths in which roughly one-half of the cells had undergone anaplastic transformation and in which mitotic figures were present, averaging at least one in every other high-power field. Finally in the "grade 4" category they included the growths characterized by marked anaplastic transformation, with bizarre pleomorphic changes in cytoplasm and nuclei, abundant polymorphonucleated and multinucleated giant cells, and pronounced mitotic activity.

Within the boundaries of this classification, it is evident that the malignancy in our case fits in well between the grade 3 and 4 categories. The short duration of the symptoms and the age of the patient correlate with the grade of malignancy. Kernohan[8] and his group have produced evidence to show that there is a direct relationship between the degree of malignancy of the neoplasm and its life history, namely preoperative duration of symptoms and

postoperative survival period. In Svien's[9] series of 161 cases, the average preoperative duration of symptoms was 20.8 months in the grade 1 malignancies, 7.3 in the grade 4 category, and 11.2 and 11.8 months in the grade 2 and 3 categories, respectively. Striking behavioristic difference was also shown in the three year postoperative survival rate, which ranged from 62.5 per cent in the grade 1 category to 3.8 per cent in the grade 4 group.

Whereas in our case most of the tumor was composed of highly anaplastic astrocytic elements, an area was accidentally found which was composed almost entirely of normal-appearing, sparsely-arranged astrocytes with homogeneous nuclei, varying numbers of fairly well formed processes, and abundant fibrillary development (figure 3). Even in this area of less cellular dedifferentiation, the normal composition and architecture of the brain tissue was absent and the number of astrocytes was materially increased over the number of astrocytes expected to be found in the corresponding zone of normal brain. In between the neoplastic cells, calcium deposits were noticed here and there and heavy deposition of lime salts had occurred in the wall of blood channels (figure 4). Microscopic deposits of calcium are fairly common in well-differentiated astrocytoma, but are rarely present in sufficient amount to be discernible on roentgenographic examination of the head. Mabon[10] found calcium recognizable roentgenographically in only seven of his 115 cases of cerebellar astrocytoma grade 1, whereas in the same series calcium deposits were seen microscopically in 14 additional instances.

The detection in our case of well-differentiated neoplastic astrocytes within an otherwise poorly-differentiated tumor suggests an origin of the latter from a preexisting astrocytoma of lower grade. This is well in keeping with the present concept that astrocytoma, astroblastoma, and glioblastoma multiforme represent various degrees of dedifferentiation of the same type of cell, the astrocyte. Scherer[11] has pointed out the not infrequent finding of foci of highly anaplastic cells within well-differentiated astrocytomas, and Kernohan[8] has repeatedly indicated that, even within the most malignant astrocytomas, careful histologic studies with special stains will occasionally demonstrate intermingling of cells in various stages of anaplasia.

In the Bailey and Cushing[6] series, there are several instances of tumors partially extirpated at successive sessions, which were classified as protoplasmic astrocytomas when first seen and later displayed cellular dedifferentiation with corresponding increase in rapidity of growth. This possibility has been confirmed by several investigators. The demonstration by Canti, Bland, and Russell[12] that cells of cultured glioblastoma multiforme pass over in time into astrocytes emphasizes further the interrelationship within this tumor-group-complex and explains the possibility of gradual transition from least malignant to most malignant types of growths.

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CASE REPORT

Gliomatosis Cerebri

Jose Bebin, M.D., Ph.D. and John S. Tytus, M.D.

NEVIN[1] in 1938 described three cases under the name of "gliomatosis cerebri," characterized pathologically by a diffuse cellular overgrowth throughout wide areas of the cerebral hemispheres, which he considered to be the result of a primary blastomatous malformation arising presumably from a congenital developmental defect.

The first case was a 23 year old female who had progressive symptoms of failing memory, mental deterioration, and epileptic attacks, and who showed signs of increased intracranial pressure with papilledema. She died shortly after a lumbar puncture and ventriculography. The second case was a 54 year old woman with history of life-long epilepsy and extensive areas of pigmentation of the skin similar to the cutaneous pigmentation of von Recklinghausen's disease, who in the last four years had shown progressive mental deterioration, and six months prior to her death developed a right hemiplegia and signs of increased intracranial pressure. She was stuporous upon admission to the hospital and died 24 hours later. The third case was a 27 year old man who had convulsions, failure of memory, and symptoms of increased intracranial pressure of two and one-half years duration. He died one year after a decompressive operation.

The postmortem examination of these three cases disclosed macroscopically only mild to moderate changes, consisting of enlargement, discoloration, and a honeycombed appearance of various parts of the brain tissue. Microscopically there was a diffuse overgrowth of neuroglial cells in all stages of development throughout wide areas of the cerebral hemispheres, with little or no tendency to local tumor growth.

Prior to Nevin's publication, similar cases had been described in the medical literature by different authors under various designations: Landau[2] in 1910, "diffuse glioma of the brain;" Hildebrandt,[3] "gliomatous hypertrophy;" Schwartz and Klauer,[4] "diffuse systemic overgrowth of the glial apparatus of the brain;" Cassirer and Levy,[5] "diffuse sclerosis of the brain with glioblastoma," Foerster and Gagel,[6] "central diffuse schwannosis in von Recklinghausen's disease;" and von Santha,[7] under a similar name. To these cases were added subsequently the cases reported by Scheinker,[8] Scheinker and Evans,[9] Malamud, Wise and Jones,[10] and more recently an interesting case reported by Moore,[11] in which this process was masked by syphilis. The contro-

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versial aspects of the histogenesis and diagnosis of this condition seem to justify the clinicopathologic report of an additional case.

REPORT OF CASE

A 44 year old, right-handed, white male was admitted to the hospital on March 21, 1954. He had complained of intermittent episodes of vertigo for two years prior to admission. The attacks lasted for five or ten minutes and were unassociated with loss of consciousness, headache, or other symptoms. He was entirely asymptomatic between attacks until eight months prior to admission when he began to complain of blurring vision. This symptom persisted and for six weeks prior to admission there was progressive mental deterioration; at the time of admission he was completely confused and disoriented with a marked memory loss for recent events. This patient was a college graduate, having majored in American history. He had a very responsible position as a director of personnel. He was a steady and dependable worker. His social adjustment was considered good. This patient's past history was completely noncontributory. There was no familial disease of any consequence.

Physical examination revealed a well-developed, well-nourished, white male in no distress but disoriented mentally. The blood pressure was 110/85, respirations were 16, and the pulse was 60. The general physical examination was within normal limits. Neurologic examination revealed complete disorientation, with very poor memory for recent events and only fair memory for past events. The funduscopic examination revealed blurred hyperemic disks bilaterally which were only suggestive of papilledema. The visual fields were normal. The other cranial nerves were within normal limits. All modalities of sensation were intact. There was no motor weakness nor were abnormal movements discernible. The deep tendon reflexes were equal and active bilaterally without pathologic signs.

The admission blood count and urinalysis were within normal limits. Examination of the cerebrospinal fluid revealed the Kahn serologic reaction to be negative. The total protein was 94 mg. per cent. The globulin was 31. The colloidal gold and mastic curves were normal. Routine skull films showed no abnormality.

On March 24, bilateral internal carotid arteriograms were performed which were believed to be within normal limits. A ventriculogram was performed on March 27. On opening the dura, there did not appear to be any brain swelling or evidence of increased intracranial pressure. The ventricular needle was passed without striking any unusual resistance on the left; 40 cc. of cerebrospinal fluid were removed and replaced with an equal volume of air. The right lateral ventricle was tapped and 50 cc. of air were injected under pressure. The ventriculogram (figure 1) revealed a widening of the corpus callosum and thickening of this

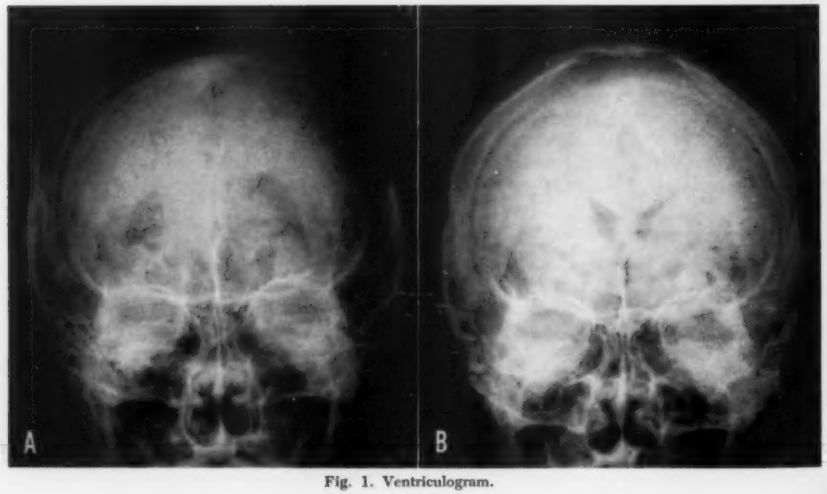

Fig. 1. Ventriculogram.

structure which was interpreted as diagnostic of a corpus callosum neoplasm. The septum pellucidum appeared to be markedly thickened. There was also a questionable minimal concave defect in the superior portions of the anterior horn of the lateral ventricles. It was believed that this lesion was diffuse glioma involving the corpus callosum and that it was inoperable. The patient was discharged on April 8 to the Traverse City State Hospital. At the time of discharge he was essentially unchanged and his condition deteriorated progressively. On May 11 he was examined and failed to reveal any signs of increased intracranial pressure. He was mute and completely inaccessible. It was thought that this represented an aphasia, primarily motor but with some receptive elements. There was weakness of the right side of the face. The deep tendon reflexes were equal and active without pathologic signs. On June 4 the patient had a generalized convulsive seizure and on June 8 he expired.

An autopsy was performed and, in addition to the central nervous system findings to be described below, there was: 1) myocardial hypertrophy, especially of the left ventricle, 2) coronary sclerosis with recent myocardial infarcts, 3) pulmonary edema and congestion, 4) hepatomegaly, 5) splenomegaly, and 6) acute passive congestion of all organs.

The brain weighed 1,600 gm. There was congestion and edema of the leptomeninges. The brain appeared to be edematous and swollen, with flattened gyri. When the brain was sectioned, there was edema of the gray and the white matter throughout. From the frontal to the occipital regions there was a brownish-yellowish discoloration of the white matter of the hemispheres. This was more marked in the frontal and central regions where there appeared to be symmetric areas of softening in the centrum ovalis. This discoloration was quite pronounced in the neighborhood of the lateral ventricles and in the region of the basal ganglia. The corpus callosum appeared thickened and the entire ventricular system was somewhat compressed. Sections of the brainstem and cerebellum revealed no gross abnormalities except for congestion and edema. The blood vessels of the brain and of the circle of Willis were normal.

Histologic description. Sections of different parts of the brain were prepared and embedded in parafin. They were stained with hematoxylin and eosin, Weil, Mallory, and Bodian technics. Frozen sections were stained by the silver carbonate technics of Rio-Hortega. Red oil was used as a fat stain. Histologically the lesions were more extensive and diffuse than was suspected from gross examination. They involved almost the entire cerebral hemispheres, but predominated in the white matter of the frontal lobes and in the basal ganglia region bilaterally.

The examination of myelin preparations at lower power magnification and even with the naked eye showed a diffuse demyelination of the white substance of the cerebral hemi-

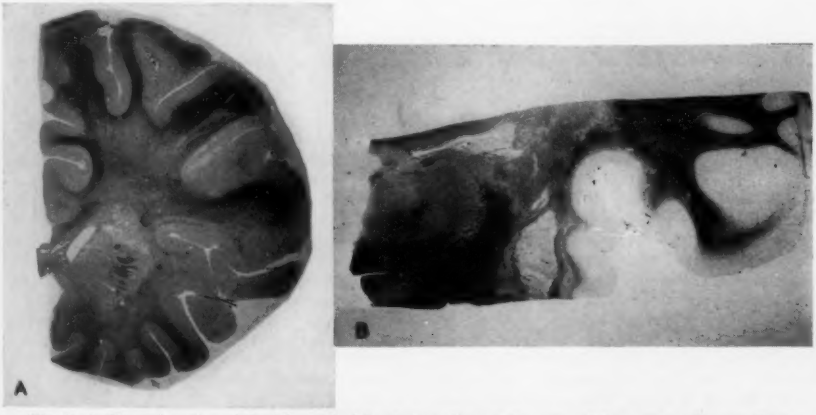

Fig. 2. *A.* Coronal section of the left cerebral hemisphere through the genu of the corpus callosum. There is marked demyelination of the white matter of the hemisphere. (Weigert's stain). *B.* Section including the thalamus internal capsule and basal ganglia, showing areas of demyelination in the internal capsule and adjacent regions (Weigert stain).

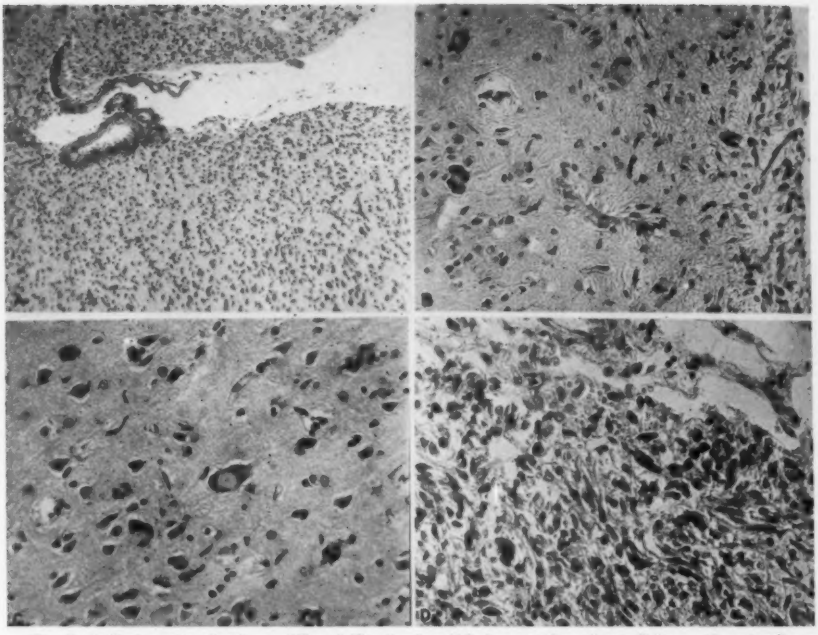

Fig. 3. *A.* Brain cortex showing a diffuse infiltration by glial elements throughout all layers (hematoxylin stain). *B.* Section of cortex. There is diffuse infiltration of glial cells, some of which are large multinucleated elements (hematoxylin-eosin stain). *C.* Brain cortex. Many of the neoplastic elements diffusely distributed through the cortex are situated as satellites of the remaining nerve cells (hematoxylin-eosin stain). *D.* Brain cortex, marginal zone. There is marked infiltration of the stratum zonale and adjacent pia mater by glial elements, mostly elongated forms (hematoxylin-eosin stain).

spheres. This change was particularly striking in the centrum ovalis and corona radiata, extending for a short distance into the white substance of the cerebral convolutions (figure 2). The demyelinating process included also a portion of the anterior limb of the internal capsule, the body of the corpus callosum, part of the basal ganglia, and, to a less degree, the thalamic nuclei. Examination under medium power magnification revealed a honey-combed appearance of the white matter of the hemispheres. This appearance was more marked in the central portion of the frontal lobe and in the basal ganglia region, particularly in the lentiform nucleus where the larger spaces become confluent to form cavities. These cavities were irregular in shape and represented large areas of necrosis. They contained abundant gitter cells and debris of the destroyed nervous substance. Here the breakdown of myelin sheaths and axis-cylinders was complete. The brainstem, cerebellum, and upper segments of the spinal cord appeared to be normally myelinated.

The preparations stained with the hematoxilineosine, Mallory, and silver technics showed moderate thickening and fibroblastic changes in the leptomeninges. In many areas the pia mater of the convexity and medial surface of the frontal lobes was diffusely infiltrated by neoplastic glial cells (figure 3D). These elements consisted mainly of elongated cells with small and medium sized dark stained nuclei, irregularly distributed about the leptomeningeal blood vessels which themselves showed hypertrophy of their walls. These glial elements resembled the so-called bipolar and unipolar spongioblasts. The preparations stained with silver carbonate demonstrated well the processes of these elements and confirmed their glial origin.

The brain cortex was infiltrated diffusely by similar neoplastic cells. This change was more pronounced in the severely involved areas, par-

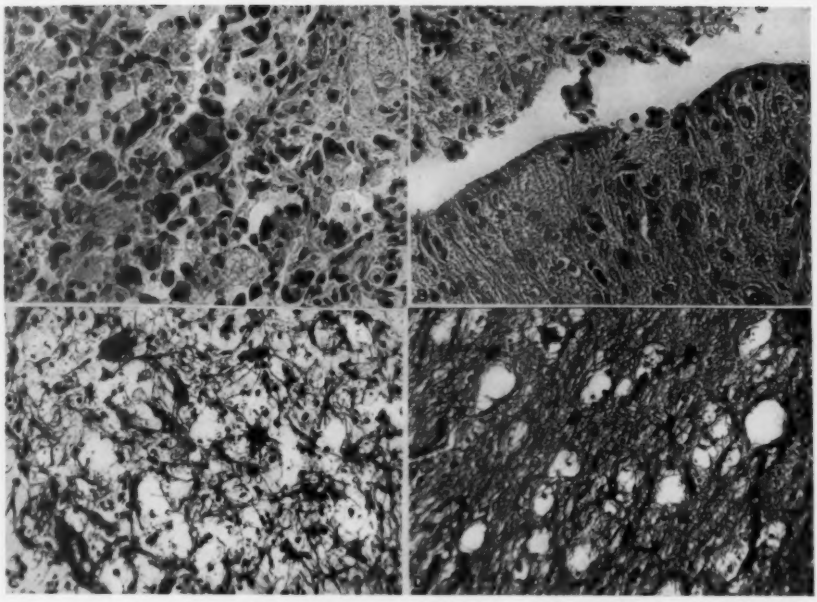

Fig. 4. *A.* Lentiform nucleus showing replacement of normal structures by neoplastic glial cells resembling a glioblastoma multiforme (hematoxylin-eosin stain). *B.* Ependyma of the lateral ventricle. There is invasion of the ependymal plate by the glial overgrowth (Mallory stain). *C.* Lentiform nucleus. There is a honey-combed appearance with formation of cystic cavities with dense glial network, monster astrocytes, and numerous gitter cells. (silver carbonate stain).

ticularly the frontal lobes and the cingulum gyri. This infiltration extended from the most superficial layer through the thickening of the cortex into the white substance of the cerebral hemispheres, changing the normally smooth appearance of the cerebral convolutions into an irregular, rough surface. The neoplastic elements infiltrating the cortex were very pleomorphic. They contained dark-stained nuclei, some of them normal in appearance, others bizarre and abnormal representing transitional anaplastic types of glial cells. These included spongioblasts, astroblasts, and well differentiated astrocytes of fibrillar and protoplasmic varieties. Numerous multinucleated giant glial cells were present throughout (figure 3B). Frequently these cells appeared as satellites of the cortical neurons (figure 3C); others were distributed diffusely, some located around blood vessels.

At low power magnification the cytoarchitecture of the cortex appeared to be preserved, but under higher power there was a distortion in the orientation and arrangement of the cortical neurons, and in many instances a loss of ganglion cells. (figure 3A).

In the more affected areas of the white matter of the cerebral hemispheres similar findings were noted. Here, however, the pleomorphism of the glial elements was most marked. Most of these cells corresponded to transitional forms and abundant multinucleated giant cells of the type seen frequently in glioblastoma multiforme with numerous examples of mitotic and amitotic division. In these areas the appearance resembled very much that of a glioblastoma multiforme. The cystic areas of necrosis previously observed in the basal ganglia region contained numerous gitter-cells with their cytoplasm filled with lipoid substances of the destroyed myelin sheaths and other nervous structures. This is well demonstrated by the silver impregnations counterstained with red oil. The silver preparations also revealed a fine network of fibers crossing these spaces and surrounding the macrophages. Within them large astrocytes were also found. The walls of these cavities were irregular and contained

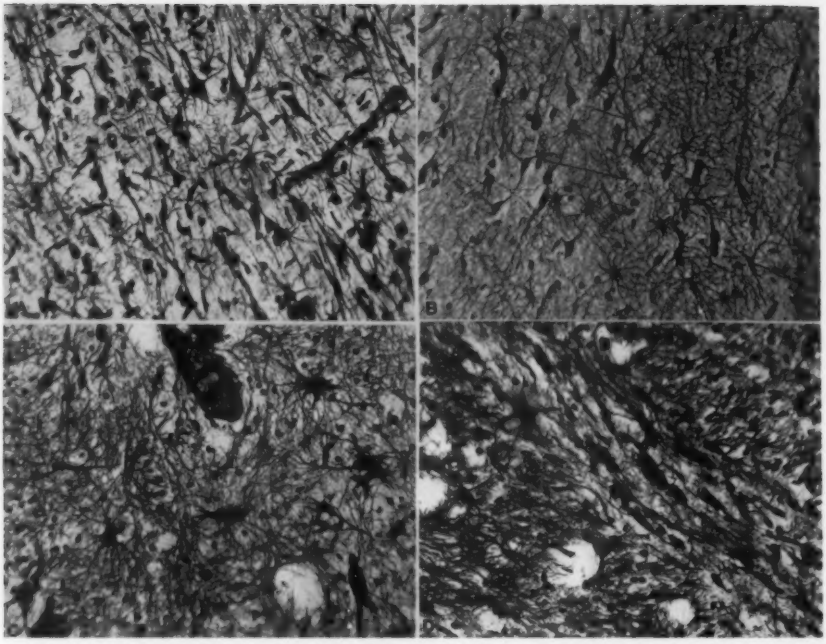

Fig. 5. *A and B.* Brain cortex. Diffuse infiltration by glial cells is well demonstrated by the silver carbonate stain. *C.* Putamen. Formation of small cystic areas has occurred which are surrounded by a dense network of glial fibers and which contain monster astrocytes and abundant gitter cells (silver carbonate stain). *D.* Internal capsule diffusely infiltrated by elongated glial elements (unipolar and bipolar spongioblasts) (silver carbonate stain).

numerous blood vessels with hypertrophied walls, abundant connective tissue, and neoplastic glial elements (figures 4 and 5).

This same diffuse glial infiltration invaded the basal ganglia, particularly the putamen. It also extended into the deeper portions of the brain invading the ependymal lining of the lateral ventricles and replacing the epithelium by abnormal glial cells (figure 4B).

The thalamic nuclei show similar changes but to a much lesser degree. Here, however, the cells were more uniform and consisted mostly of bipolar or elongated forms with few multinucleated elements. In the temporal lobe and to a certain extent in the occipital lobe, there were similar pathologic changes, but these were only moderate compared to the changes observed in the frontal lobe and basal ganglia region. In the periventricular zone of the temporal lobe, particularly in the neighborhood of the roof of the temporal horn of the lateral ventricle, in addition to the already described changes, there were abundant clusters of mononuclear elements (lymphocytes and plasma cells) arranged perivascularly.

In the brainstem (midbrain, pons, and medulla) and in the cerebellum there were no pathologic changes other than acute passive congestion and edema. A small blood clot was found in the floor of the fourth ventricle.

In general the lesions in the various affected areas of the brain were found histologically to be almost identical in appearance. Nevertheless the degree of involvement varied somewhat from one zone to another. In the frontal lobe and the basal ganglia, where this process was most pronounced, the appearance resembled very much that of a glioblastoma multiforme. In the areas that were involved less extensively (thalamus, temporal, and occipital lobes), the process seemed to resemble more closely that of a spongioblastoma or an astrocytoma. The brainstem and the cerebellum were free of this neoplastic invasion.

COMMENT

According to Scheinker,[8] two types of "gliomatosis cerebri" can be distinguished from the standpoint of localization and clinical symptomatology: 1) the brainstem type, and 2) the hemispherical type. A third type may be added which includes the diffuse dissemination of the process throughout the entire nervous system, diffuse cerebrospinal gliomatosis.[11] In all types the pathologic process is the same. Grossly the main change is a diffuse enlargement or hypertrophy of the affected regions with preservation of the general configuration. There is widespread, diffuse extension of the pathologic process with no demarcation between normal and involved areas. The principal microscopic characteristics consist of a neoplastic proliferation of glial elements infiltrating diffusely among normal structures, and destruction of myelin sheaths with slight or no damage to nerve cells and axiscylinders, without secondary degeneration.

From the clinical history, course, and postmortem findings there is no doubt that the present case belongs to this group of disorders, particularly to the second type. In our case the diffuse infiltration of neoplastic cells was observed mainly in the cerebral hemispheres, especially in the frontal and basal ganglia regions bilaterally. In these areas the process resembled very much that of a glioblastoma multiforme, but in the areas that were less involved the pathologic changes were more characteristic of spongioblastoma or astrocytoma. The histogenesis of this process has been debated extensively. The main problem seems to be whether or not the genesis and the growth of the glial cells take place under the same conditions that are prevalent in circumscribed gliomas. The majority of authors regard this condition as a developmental anomaly of the neuroglia rather than as a true neoplasm. Landau[2] thought that the pathologic changes were due to a development *in situ* of the glial cells and not due to infiltration. This opinion is shared by Scheinker.[8,9] Nevin[1] in his detailed study regarded this condition "not as a neoplasm in the strict sense of the term, but as a blastomatous malformation, in some way or other congenitally predetermined," but he himself recognized the difficulties and the impossibility of defining the boundaries between malformation and true tumor formation. In conclusion, he considered the cases that he described as well as those cases collected from the literature, as forming a distinct group, closely related pathologically, but with wide variation in the microscopical details. However, the onset of this condition in adult life and its rapid progressive course with signs of increased intracranial pressure speak strongly in favor of a neoplastic origin, as Malamud and associates[10] suggest. In the present report the patient's illness began at the age of 43 and he died 11 months later, as do most patients with malignant gliomas. In addition the morphologic resemblance of the histologic changes in this process to the pathologic findings in these gliomas is strong argument in favor of the hypothesis that this condition is a true neoplasm. The widespread and diffuse involvement of the central nervous system is interpreted by Moore[11] as the expression of "tissue vulnerability" to neoplastic glial cells, in which there is a receptive "chemical soil" to their overgrowth, in contrast to the circumscribed glial tumors in which the surrounding tissue possesses varying degrees of resistance.

The nomenclature employed to describe this condition has varied considerably in the literature. Nevin[1] considered the term "gliomatosis cerebri" the "most suitable for the entire group of cases;" Scheinker[9] preferred the term "glioblastosis cerebri diffuse" as being more descriptive. The latter name excludes the diffuse glial involvement by mature glial cells described by Elvidge, Penfield, and Cone[12] as "astrocytoma diffusum," and the "patchy blastomatous infiltration of the central nervous system" described by Ferraro and associates.[13] Moore[11] considered that "diffuse cerebrospinal gliomatosis" would be a more desirable designa-

tion for this widely spread glial overgrowth.

The most significant difference between gliomatosis cerebri and astrocytoma diffusum is that in the latter the cells are mature and consist of astrocytes, and in the former cells of this type are occasionally found but anaplastic and transitional forms of glial cells predominate. In astrocytoma diffusum the process remains localized to the hemispheres, whereas the neoplastic proliferation in gliomatosis cerebri extends over widespread areas throughout the entire central nervous system or even beneath the leptomeninges, as described in the cases of Nevin[1] and in our case.

In some cases of gliomatosis cerebri the pathologic process produces a diffuse demyelination which has been interpreted as Schilder's disease. Other cases of the patchy type of gliomatosis associated with this demyelination have been interpreted as transitional stages between multiple sclerosis and neoplasm. Blastomatous glial proliferation is not usually present in Schilder's disease, and degenerative and inflammatory phenomena are foreign to gliomatosis cerebri.

From a therapeutic point of view, little can be done to help patients with this condition. Decompression operations have a paliative effect of short duration. Malamud and associates[10] believed that deep x-radiation was of some benefit to their patient. Perhaps other forms of irradiation[14] such as cobalt or $boron_{10}$ may prove more effective.

SUMMARY

A clinicopathologic study of a case of gliomatosis cerebri is described in a 44 year old man who had attacks with loss of consciousness, vertigo, and progressive mental deterioration without focal signs. He died 11 months after onset of symptoms. Postmortem examination disclosed increased weight of the brain and edema. Histologic examination revealed extensive demyelination of the white substance of the hemispheres and diffuse infiltration of the cerebral hemispheres by neoplastic glial cells. This process in the frontal lobes and basal ganglia regions resembles that of a glioblastoma multiforme. In the less involved areas (thalamus, temporal, and occipital lobes), the process resembles that of a spongioblastoma or astrocytoma. The brainstem and cerebellum were free of this neoplastic invasion. Pathogenesis of this process is discussed.

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CASE REPORT

Occlusion of the Basilar Artery

Diagnosis by Vertebral Angiography During Life

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THE PURPOSE of this report is to draw attention to the fact that diagnosis of occlusion of the basilar artery can be made during life by means of percutaneous angiography. So far as we are aware, this is the first time that this condition has been demonstrated by angiography. This method of investigation is a useful additional means in our efforts to make a differential diagnosis as early as possible.

REVIEW OF THE LITERATURE

Vascular lesions affecting the posterior part of the brain have always attracted the attention of neurologic clinicians and pathoanatomists. The first communications on occlusion of the basilar artery appeared during the latter half of the last century. These were in the main based on cases of syphilitic origin. In 1868 Hayem[1] described the pathoanatomic changes in a case of occluded basilar artery, without giving details as to the clinical manifestations. A few years later in 1875 Leyden[2] reported two cases with necropsy, both displaying thrombotic occlusion of the basilar artery, probably due to syphilitic arteritis. In the two cases the major clinical manifestations were a sudden onset of hemiplegic disorders progressing to quadriplegia, associated with signs of bulbar affection, disorders of the conjugate movements of the eyes, anisocoria, and no pupillary reaction to light. In both cases coma supervened, and death occurred within 24 hours in the one case and in the course of a few days in the other. Leyden stressed that, of the several arteries, the basilar is a favored seat of syphilitic changes.

In 1912 Marburg[3] presented a thorough exposition of the localization of lesions affecting the pons and the medulla, together with a correlation of the anatomic changes with signs and symptoms from the cranial nerves.

In communications from the last decades atherosclerosis has been taken to be the main genetic factor. This has been emphasized by L'hermitte and Trelles[4] and more recently by Kubik and Adams[5] in the largest series so far published. In 7,400 consecutive autopsies 25 cases of occlusion of the basilar artery were disclosed by the latter writers, that is an incidence of one out of 300 autopsies.

Until 1946 the diagnosis was made at autopsy in all cases. Kubik and Adams were the first to suggest the possibility of

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making a diagnosis during life. They mentioned four cases in which this has been done. Since then a single case history has been recorded by Freemann, Ellis, and Knox,[6] in which an occlusion of the basilar artery has been suggested; in this case the patient recovered.

In the two cases reported here a diagnosis of occlusion of the basilar artery was made first on the basis of the clinical manifestation. This was later corroborated by vertebral arteriography. This latter mode of corroboration or verification has not, so far as we are aware, been described before.

CASE REPORTS

Case 1. A 44 year old taxi-driver with no history of syphilitic infection, heart disease, depressive states, or carbon monoxide intoxication was hospitalized August 4, 1951.

For a few months before hospitalization it had become increasingly difficult to arouse the patient in the night, according to his wife. The day before the onset of symptoms he had worked with no complaint. The following day he could not be aroused in the morning. He was admitted to his regional hospital, where examination gave the following findings: A deeply somnolent (comatose) patient, with mild respiratory embarrassment, no physical disorders, temperature 37° C., pulse rate 52 per minute. Generalized loss of muscular tone; no stiffness of the neck; dilatation of the pupils with no reaction to light. The corneal reflexes were elicitable; no abnormalities of the fundi; flaccidity of the limbs; the triceps and patellar jerks could be elicited; no Babinski response. Cerebrospinal fluid showed normal cell count and protein content and no pressure variations. Electrocardiogram, blood urea, urine sedimentation, and blood sugar tests revealed no abnormalities. Penicillin was administered because of a rise in temperature to a maximum of 38.5° C. This abated after a fortnight, followed by a recurrent rise in temperature which disappeared after a second period of penicillin administration.

Ten days after the onset, neurologic examination revealed the following: He was still soporous; there was marked dilatation of the pupils with no reaction to light; no stiffness of the neck; abdominal reflexes could not be elicited; marked relaxation of muscular tone in the limbs; deep reflexes were all equally weak on the two sides. The plantar response was elicitable with difficulty, but normal in type.

Three weeks after the onset, he was admitted to the present department of neurosurgery. On admission he was unclear mentally. He was unable to give his name. There was an abduction of the right eye, no reaction to light of the pupils; questionable lower facial weakness of the right. He was able to move his limbs. Ventriculography revealed an intracranial fluid pressure of 40 to 60 mm. of water. A mild dilatation of the entire ventricular system was disclosed in the pneumograms; this was slightly more marked in the left. The left temporal horn was questionably displaced downward and medially. An intracerebral hemorrhage was suggested and an exploratory craniotomy was performed, exposing the left temporal lobe. No hematoma was found. The cerebral fluid showed normal cell count and protein content. Postoperatively, an additional difficulty in moving the right-sided limbs was disclosed, together with a mild increase in right-sided deep reflexes; the plantar responses remained normal. At a later stage left and right carotid angiography was performed, revealing a normal cerebral vascualr tree apart from mild caliber variations of the arterial trunks.

At this stage six weeks had passed since the onset of the disease; during the following two months the patient was admitted to the neurologic department. His condition improved gradually, so that eventually he was oriented as to place and the persons attending him; he was able to react appropriately on verbal communication with sentences; speech was slow and slurred; he was unable to recall anything occurring within the first months of his disease. He was emotionally unstable, with a tendency to cry. Double lumbar puncture showed a mild increase in the spinal fluid protein content (six weeks after craniotomy) and normal cell count. The suprarenine-fluid-sugar test: 0.008 (abnormal reaction). Percentage quotient 60; spinal sugar 56 to 64. Wassermann reaction in blood and spinal fluid negative. Blood pressure 120/70. Electroencephalogram showed decreasing dysrhythmia on repeated examination (after operation). This was more marked on the left where some additional abnormal slow waves of 3 to 5 cycles per sec. were found. The dominant activity was 6 to 8 cycles per sec. and in the left 7 to 9 cycles per sec. The alpha rhythm was generalized; focal leads suggested a localized process in the middle or posterior parts of the left hemisphere. Ophthalmologic examination showed visual acuity normal on both sides; 15° adduction of the right eye; no ptosis. The pupillary diameter was 5 mm. on the two sides. There was a mild reaction to light on the left involving the entire inner pupillary border; on the right only a weak reaction to light was

disclosed, involving exclusively the temporal half of the pupil; convergence reaction was difficult to evaluate; lateral movements of the eyes were unimpeded; in particular no paresis of the right internal rectus muscle could be found. Vertical movements could not be elicited either upward or downward. No abnormalities were revealed on ophthalmoscopic examination; in particular, there was no sclerosis of the vessels; the visual field was normal; no nystagmus.

On neurologic examination a mild lower facial weakness on the right was found, and the abdominal and cremasteric reflexes could not be elicited. There was a generalized muscular atrophy and relaxation of the muscular tone of the limbs, mild powerlessness of the right arm and leg, and mild exaggeration of the deep reflexes. Plantar responses were normal but weak; there were mild disorders of coordination and bilateral impairment of rapid alternating movements; he could walk with support.

Summary. A man age 44, in the course of one night, developed marked disorders of consciousness, generalized muscular relaxation, and dilatation of the pupils with no reaction to light.

In the course of three months there was a gradual improvement in his condition, leaving a residual Parinaud's syndrome and mild loss of power and tone in the right arm and leg.

Discussion. From the viewpoint of making a diagnosis, encephalitis and a vascular process in the brainstem must be taken into consideration.

In his monograph on epidemic chronic encephalitis, Wimmer[7] has reported case histories of somnolence and clouded consciousness lasting for months and years. In all cases the onset was less sudden than in the present case, and the course was remitting. Similar observations have been made by Neal.[8] In these cases also, ophthalmoplegia has been described involving gaze paralyses, both on look upward and downward, together with disorders of the pupillary reflexes varying in the course of disease often from one day to another.

Wimmer emphasized that a paresis of accommodation would suggest a diagnosis of chronic epidemic encephalitis, if cerebrospinal syphilis can be precluded. Werniche's polioencephalitis hemorrhagica superior usually has a fatal course within a few days. The present patient was not an alcoholic.

The mild rise in temperature during the initial phase of the disease and the abnormal reaction of the suprarenine-fluid-sugar test favors a diagnosis of encephalitis. These disorders are taken to be the result of metabolic changes following a diminution of circulation within the area of the basilar artery.[9,10]

Turning then to a probable vascular genesis, the question arises whether we are concerned with a hemorrhagic, an embolic, or a thrombotic lesion within the area of the basilar artery. In the case of hemorrhage it might be expected that sooner or later blood will appear in the spinal fluid. It should be recalled that at no stage blood, xanthochromia, or pleocytosis were found. The increase in protein content appeared first after exploratory craniotomy involving several punctures of the left temporal lobe.

As evidence against an embolic occlusion in the area of the basilar artery, the absence of pulmonary and cardiac diseases both in the history and on examination must be stressed. There remains to be considered the question of a thrombotic occlusion. The fact that the onset of symptoms occurred during sleep favors a thrombosis. At certain stages during sleep there is a diminution of the blood flow rate through the brain. As has been mentioned above, L'hermitte and Trelle[4] and Kubic and Adams,[5] among others, have found that in large series the basilar artery is the seat of early atherosclerotic changes, usually occurring before similar changes in other large cerebral arterial trunks. The age of the present patient—44 years—does not preclude the presence of an atherosclerotic lesion. The radial arteries were stiff and rigid. Carotid angiography showed variations of the caliber of the carotid syphon on both sides. This must be taken as an indication of atheromatosis of the internal carotid arteries.

Symptomatology. The symptoms in the present case may well be explained on the basis of localized ischemia in the brainstem. Usually the presence of Parinaud's syndrome is taken to result from a lesion of the lamina quadrigemina. According to Behr,[11] this structure receives its blood supply from the superior cerebellar artery and the posterior cerebral artery, that is to say, branches from the basilar artery. The pyramidal symptoms result from lesions of these parts of the brainstem. That severe disorders of consciousness occur in lesions of the area in consideration has often been shown in experimental animals. It is also well known that traumatic brainstem lesions, either mediately or immediately following transtentorial herniation and cerebral edema, may result in a clinical picture which is indistinguishable from that seen in the present case. Evans,[12] in his book on acute head injuries, mentioned a case of a young man who, after transtentorial herniation of the brainstem, lived as a decerebrated specimen five years after the injury.

Vertebral angiography. In the attempt to

corroborate a diagnosis of basilar occlusion, a percutaneous vertebral arteriography was performed three months after the onset of disease. The arteriogram showed dense filling of the vertebral artery in the anteroposterior films. There were only traces of contrast medium to be seen in the basilar artery, while the peripheral branches, that is, the posterior cerebral arteries and superior cerebellar arteries, were distinctly filled, a little more on the right than on the left. This concurrence of central and peripheral filling must be taken as an incomplete occlusion of the lumen of the basilar artery.

Case 2. A 65 year old man was hospitalized April 19, 1954 and discharged on April 28, 1954. He had a predisposition to migraine. In childhood he had had lupus which was cured by light treatment, together with osseous tuberculosis, followed by anklosis in the left elbow joint. He had never had venereal disease. For a few years before admission he had complained of a nearly constant sensation of cold in the lateral toes of both feet. For about 15 years he had had spells of tingling and numbness in the top of his head, followed by disorders of speech such as difficulty in articulating. These attacks were never associated with facial weakness or signs and symptoms from the limbs. There was a rapid improvement after the administration of ergotamine drugs, usually in the course of a few minutes.

During the last few months before admission he had had eight or nine attacks lasting a few minutes, during which he had a marked vertigo with a sensation of rotation of the surroundings to the right, dysarthria, left lower facial weakness, and weakness in the left arm and leg. He recovered completely from these attacks in a few minutes. Between attacks he felt well and there were no complaints of loss of memory, increased fatigability, or cardiac symptoms.

He was a heavily built man; his mental state was normal; he was intelligent and no mental reduction could be disclosed. An arcus senilis was found in both eyes. There was a deviation of the tongue to the right; the left upper limb was hypoplastic, but the motor power of the hand was good. Ophthalmologic examination revealed narrowed and shining arteries in both fundi; apart from this no abnormalities could be disclosed. Otologic examination revealed deafness for high pitched sounds, as might be expected at his age. No vestibular disorders were found. The electrocardiogram showed left axis deviation. The electroencephalogram showed moderate to medium generalized dysrhythmia with slow waves of 6 to 7 cycles per sec., no paroxysms, no high voltage, and no focal changes. The blood pressure varied from 165/95 to 145/100. Wassermann reaction in blood was negative.

Summary. A man of 65 with a mild arterial hypertension, within one month before admission, had had vertiginous spells, attacks of dysarthria, and rapid transient attacks of loss of power in the left-sided limbs. Each attack was followed by a complete recovery.

Discussion. The history is so indicative of a vascular lesion as the cause that other possibilities may be nearly ignored. The symptoms were taken to result from vascular cerebral insufficiency, probably spasm in atherosclerotic vessels.

Angiography. Since an intracranial space-taking lesion could not be precluded, angiograms were made after injection into the right common carotid artery. The films showed marked atheromatous changes principally in the carotid system. There was no displacement of the large arterial trunks; in the anteroposterior view, the anterior cerebral artery was seen exactly in the midline. The posterior communicating arteries were filled and so were the two posterior cerebral arteries and the two superior cerebellar arteries, and a reflux was demonstrable into the basilar artery for about an inch, indicating severe circulatory disorders in the posterior fossa. The phlebograms revealed no abnormalities. Half an hour after this procedure, which was done without immediate complications, a sudden collapse developed. The patient lost consciousness; there was a complete respiratory stop and artificial respiration was started. Despite this effort, the patient died 48 hours later without recovering consciousness.

At autopsy, severe changes were found in the heart, namely a newly formed infarction, marked fibrosis, and hypertrophy. Brain autopsy showed marked sclerosis and complete thrombosis of the basilar artery. In the medulla a newly formed red infarction was found. Additional sclerotic changes were found in the right posterior cerebral, middle cerebral, and anterior cerebral arteries. The histologic diagnosis was a thrombosis of the basilar artery and of the right posterior cerebral, middle cerebral, and anterior cerebral arteries, arteriosclerosis of the brain with infarction of the medulla, and diffuse atrophic changes on the basis of arteriosclerosis.

Symptomatology. In this case the history and the clinical findings are in agreement with the angiographic and pathoanatomic changes. The vertiginous spells may be taken to result from transitory circulatory disorders in the internal auditory artery (a branch from the basilar artery). The recurrent attacks of powerlessness in the left-sided limbs is in agreement

with the fact that the severest pathoanatomic changes were found in the right hemisphere. In view of the severe changes found in the brain and the heart at autopsy, it is reasonable to assume that at any time the patient might have developed a clinical picture like that occurring after angiography, leading to the death of the patient. It would seem unwarranted, at least without qualifications, to interpret the death of the patient as resulting directly from the angiographic intervention.

ANATOMY

The vascular supply to the pons, midbrain, and cerebellum has been investigated meticulously by Foix and Hillemann,[13] Pines and Gilinsky,[14] and L'hermitte and Trelles.[4]

After injection of dye into the basilar artery, followed by a minute examination of the brainstem, the first-named authors have described three sets of branches which are given off in a varying number from the trunk of the basilar artery: 1) from the dorsal part of the artery four to six paramedian arteries which penetrated the mesial and ventral surface of the pons supplying the underlying territories; 2) from the lateral walls of the basilar artery the short circumferential arteries shoot off, supplying the lateral three-fifths of the ventral part of the pons and the cerebral peduncles; and 3) the long circumferential arteries that, according to the above authors, should supply the lateral parts of the pons and the tegmentum pontis. While the existence and supply areas of the two first systems are well established, the third is more questionable. Pines and Gilinsky[14] maintained that after injection of dye into the basilar artery they have never been able to demonstrate the dye in the tegmentum of the pons. This part of the pons is probably supplied by the superior cerebellar arteries, as has been stated by Biemond.[15] It is well known that no changes are found in the tegmentum pontis after occlusion of the basilar artery and that neurologic signs of a lesion of the nuclei in this region cannot be demonstrated. This is thought to be due to the presence of anastomoses between the superior cerebellar artery and the posterior cerebral artery.[16]

While the basilar artery is formed by the junction of the two vertebral arteries, the two posterior cerebral arteries originate at its oral end. It should be recalled, however, that the two last-named arteries cannot be taken as endarteries, since they are connected with circulation in the carotid system via the two posterior communicating arteries.

PHYSIOLOGY

Under normal conditions, the arterial pressure in the posterior communicating artery does not exceed that of the basilar artery. Usually, in angiograms made after injection into the carotid, no contrast medium is seen in the basilar artery.[15] If the pressure in the basilar artery is lowered, for example, in the case of a partial occlusion, the territory rostral to the occlusion may be supplied via the posterior communicating artery. This is shown in the angiographic changes described in case 2. Whether this supply is sufficient is dependent on the functional state of the posterior communicating artery; this, in turn, is dependent on the arterial pressure in the carotid system and on the caliber of the posterior communicating artery. This explains the fact that thrombosis of the basilar artery does not always lead to circulatory insufficiency within the entire territory supplied by the basilar artery (the greater part of the brainstem and the cerebellum). Only those territories are affected that are supplied from the lateral branches shooting off exactly from the place where the thrombosis affects the walls of the basilar artery. This has been emphasized by Pines and Gilinsky.[14]

It becomes clear that the clinical picture of basilar artery occlusion may vary according to the degree and the site of occlusion.

SUMMARY

A survey is presented of the reported cases of occlusion of the basilar artery. Two

further cases are described. In the two cases, the diagnosis of occlusion of the basilar artery was made on the basis of the clinical changes. This was later corroborated by angiography. This type of verification has not been reported previously. In these cases there was agreement between the clinical and the angiographic findings.

This is followed by a survey of the angiographic conditions in the territory of the basilar artery, with reference to the anatomic and physiologic variations.

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■ The best means (so far as the limbs alone are concerned) to detect the existence of an unfelt aura, consists in applications of ligatures on each limb alternately. Suppose a case of epilepsy in which the fits are frequent, and come at nearly fixed times, or after warnings of any kind, so that it may be known that it is to take place in a given time or nearly so: a very tight ligature is put on one limb, and if the fit does not come, it is extremely probable that it depends on the irritation of an unfelt aura; if it comes, the ligature is applied on the other limbs at other times. I am sorry not to be able to give more details in this respect, but I think it will be easy to understand how, by such a means, it may be ascertained if an aura comes from the upper part of a limb, or from a toe or a finger, and from which one.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

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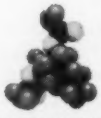

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NOVEMBER, 1956

Latest News On International Congress

Communications from Brussels indicate that program plans for the First International Congress of Neurological Sciences to be held in Brussels July 21 to 28, 1957, are now well under way (See August 1956 Newsletter for detailed preliminary announcement). The first five days (Sunday-Thursday, July 21-25), will be devoted to the seven principal topics or symposia to be presented at the congress; two major topics selected because they have a common interest to all the individual groups which have been affiliated in the congress: extrapyramidal pathology on Monday, July 22 (Prof. Raymond Garcin of Paris, topic director) and the significance and interpretation of modifications of the conscious state on Tuesday, July 23 (Sir Geoffrey Jefferson, topic director). Besides the topics of common interest, each of the individual groups affiliated in the congress* will present a topic of general interest, but one in which the individual group has special concern and competence: on Wednesday morning (July 24) multiple sclerosis, the main topic of the International Neurological Congress (Prof. H. Houston Merritt, topic director); in the afternoon, the pathologic aspects of multiple sclerosis, the topic of the Congress of Neuropathology (Dr. Armando Ferraro, topic director); on Thursday morning, petit mal epilepsy, the topic of the Congress of Electroencephalography and Clinical Neurophysiology, (Dr. Frederic A. Gibbs, topic director); and in the afternoon supratentorial angiomas and therapeutic applications of hypothermia, the topic of the Congress of Neurological Surgery in association with the Symposium Neuroradiologicum (Dr. Marcel David, topic director). The principal topic of the International League Against Epilepsy, subcortical and temporal lobe epilepsy (A. Earl Walker, topic director) will have its sessions on the first day of the congress (Sunday, July 21).... The participants in the program of topics of both common and more special interest, who have already been selected, will comprise presentations of papers (20 minutes) and 10-minute discussions (by invitation). In addition there will be opportuni-

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*The affilated groups comprising the First International Congress of Neurological Sciences are: Sixth International Neurological Congress, Third International Congress of Neuropathology, Fourth International Congress of Electroencephalography and Clinical Neurophysiology, International League Against Epilepsy, First International Congress of Neurological Surgery, and Fifth Symposium Neuroradiologicum.

ties for discussions from the floor. The presentations and discussions of principal topics will be translated simultaneously by expert interpreters for ear phone transmission in the three official languages of the Congress: English, French, and German.

Minor Topics and Free Communications Time also has been allocated for the presentation of minor topics or symposia and individual communications on Friday and Saturday (July 26-27), as well as during the first four days of the congress. Titles and abstracts of accepted communications in this category will be printed in booklets to be circulated prior to the congress and the papers will be published in extenso in the digest of the congress. Submission of titles by investigators in the basic neurologic sciences is cordially invited.

Submission of Titles, Registration, Lines of Communication, Information, Deadlines, Fees In the United States, the submission of all titles and 500-word abstracts for presentation in the program of minor topics and communications, as well as requests for registration forms and general information, except for the Congress of Neurological Surgery,* should be made to Dr Pearce Bailey, Secretary of the Committee for the United States, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland. These will be processed and forwarded to Dr. Ludo van Bogaert, Secretary-General of the First International Congress of Neurological Sciences, who with his collaborators will determine the final selection of the presentations. No presentation will be considered until registration is completed. Registration fees are: active member, $15.00, associate member, $10.00, and auxiliary member, $5.00.

National Science Foundation Announces Grants to Scientists The National Science Foundation will make available a limited number of individual grants to partially defray the travel costs of American scientists to the First International Congress of Neurological Sciences, Brussels, Belgium, July 21-28, 1957.... Application blanks may be obtained from the National Science Foundation, Washington 25, D. C. Completed applications must be received by the Foundation before January 1, 1957.

* * * * * *

NINDB Announces New Grants Program The National Institute of Neurological Diseases and Blindness announces that it is sponsoring, through grants to training institutions, a new program of postdoctoral training in the basic neurologic, ophthalmologic, and otologic sciences. Purpose of the program is to increase the number of trained basic scientists interested in pursuing academic careers in such fields as neurochemistry, neuropharmacology, neuropathology, neuroa-

*Such inquiries and communications should be sent to Dr. William B. Scoville, 85 Jefferson Street, Hartford, Conn.

natomy, ophthalmic and otologic pathology, neuroradiology, and audiology.... Funds granted for this purpose may be awarded to either clinical or basic science departments to establish or complement advanced programs in these activities. Such funds may be utilized to employ additional personnel, to pay trainee stipends, to purchase equipment and supplies, and, when necesary, for the renovation and alteration of physical facilities and necessary minor adjustments of space used in postgraduate training of investigators. Applications received after November 1 will be acted upon by the Institute's National Advisory Council in June 1957.... For further information and application forms write to the Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda 14, Maryland.

MS Society Appoints Medical Director Thomas L. Willmon, AAN associate member and formerly executive officer of the Naval Medical Research Laboratory at Bethesda, has been appointed director of the medical and scientific department of the National Multiple Sclerosis Society. He succeeds Dr. Frederick L. Stone, who has returned to the National Institutes of Health. A native of Texas, Dr. Willmon, who has been in the naval service 25 years, is known for personal research in respiratory and cardiovascular physiology and supervised a wide spectrum of basic medical research while serving in several important administrative posts in the Naval Medical Corps.

Ford Foundation Backs Brain Studies Major research studies on the human brain will be undertaken in California with backing of nearly one million dollars in Ford Foundation funds. One of the awards, in the amount of $450,000, is for an investigation of brain molecular chemistry in mental retardation to be carried on in the California Institute of Technology (Pasadena); the other, a grant of $500,000 to the UCLA School of Medicine, will concentrate on "mapping" areas of the brain controlling perception, learning, and other behavioral processes.... Dr. Linus Pauling, 1954 Nobel winner and AAN member, will direct the project at the California Institute of Technology.

New Monthly Peak Reached in Membership Campaign During the month of September, 79 additional physicians and scientists accepted invitations to AAN membership, the highest monthly figure since the campaign began last April. These new members (all categories) are: Eben Alexander, Jr., Milton Alter, William C. Baird, Louis Bakay, Ruth W. Baldwin, H. J. M. Barnett, Robert C. Bassett, R. Frederick Becker, James E. Birren, Stella Y. Botelho, Roscoe O. Brady, Patrick F. Bray, Kenneth R. Brizzee, Chandler McC. Brooks, H. S. Burr, Sam L. Clark, Donald J. Coleman, Harold F. Corson, George D. Davis, Edward D. DeLamater, Jean-Leon Desrochers, David D. Donaldson, Harry R. Draper, Donald Duncan, Roger C. Duvoisin, K. M. Earle, Robert W. Egan, Clement A. Fox, Laurence Frost, Ernest Gardner, David Green, D. J. Green, J. Francis

Hartmann, Samuel P. Hicks, Lowell E. Hokin, Barbara Hulfish, Theodore H. Ingalls, Everett H. Ingersoll, Ira J. Jackson, Thomas N. Johnson, Elvin A. Kabat, Robert Katzman, Niklaus J. A. Keller, Hermenegildo F. Labsan, Byron E. Leach, John R. Lindsay, George Margolis, Jose Mateos, Huntington Mavor, Francis C. Mayle, Jr., W. R. McCrum, G. K. Morton, Sheff D. Olinger, Jr., Norman S. Olsen, James W, Papez, Linus C. Pauling, Arthur A. Pava, John H. Perry, R. Ponce R., Bruce L. Ralston, Isabelle Rapin, Richard Raynor, Glenn V. Russell, Luis P. Sanchez-Longo, Arthur W. Schappell, Henry G. Schwartz, Alvin D. Sidell, S. R. Snodgrass, Sombut Sukondhabhant, Hartwell G. Thompson, Jr., James E. P. Toman, R. C. Truex, Samuel A. Trufant, Basil L. Truscott, Maurice Victor, J. Allan Walters, Dean D. Watt, Keasley Welch, Russell T. Woodburne.... Inquiries on AAN membership should be sent to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institute of Neurological Diseases and Blindness, Bethesda 14, Md.

Briefs On December 7 and 8, the Association for Research in Nervous and Mental Disease will hold its annual meeting at the Roosevelt Hotel, New York City. The subject of the meeting will be "The Brain and Human Behavior."..... The next examinations of the Board of Psychiatry and Neurology are scheduled for December 10 and 11 at the New York State Psychiatric Institute and the Neurological Institute.... Supported by the Muscular Dystrophy Associations of America, a program in muscular dystrophy is being developed at the University of Wisconsin under Henry A. Peter, assistant professor of neurology and psychiatry. Consultants on the program are Harry D. Bouman, Clinton N. Woolsey, and Hans H. Reese.... Philip Zenner, AAN honorary member, professor emeritus of neurology at the University of Cincinnati College of Medicine, died June 25, age 104.... Henry W. Woltman, since 1931 senior consultant in neurology at the Mayo Clinic, former president of the American Neurological Association and chairman of the A.M.A. Section on Nervous and Mental Disease (1934), retired on July 1.... The 24th series of the Thomas William Salmon Lectures will be given by Horace W. Magoun on November 15 at the New York Academy of Medicine. The subject is "The Waking Brain: the Role of the Reticular System in Wakefulness and Behavior."..... On October 24, Dr. H. Fischgold, chief electroencephalographer and chief neuroradiologist of the Saint Ann Hospital, Paris, France, gave a lecture on "Some Investigations About the Petit Mal" at NINDB.

Knott New President of EEG Society John R. Knott was named president of the American Electroencephalographic Society at its tenth annual meeting held in Atlantic City (June 15-17). Others elected to office were: Robert S. Dow, president-elect; J. K. Merlis, secretary; and Peter Kellaway, treasurer.

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(1) Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. 160:752 (Mar. 3) 1956.
(2) Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. 160:749 (Mar. 3) 1956.

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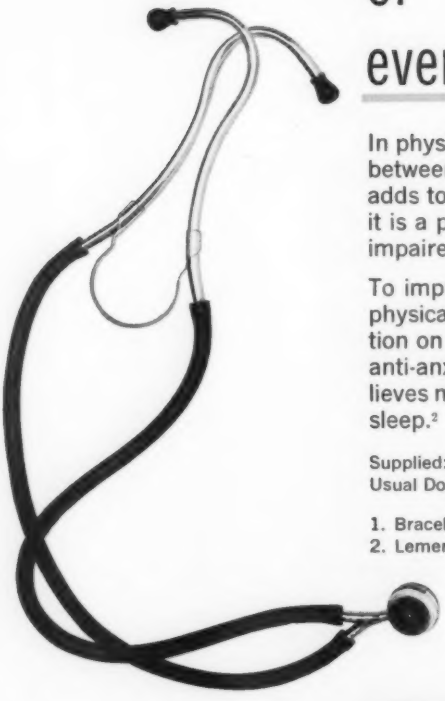

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1. Braceland, F.J.: Texas State J. Med. 51 :287 (June) 1955.
2. Lemere, F.: Northwest Med. 54 :1098 (Oct.) 1955.

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